ATLAS OF THE

SECOND EDITION

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EDITOR-IN-CHIEF

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PREFACE

This second edition of the *Atlas of the Prostate* summarizes the current evaluation and treatment of prostatic diseases. Diseases of the prostate invariably affect men as they age into their sixth decade of life and beyond, and physicians who provide care for older men invariably devote a greater portion of their clinical attention to the prostate. This Atlas conveys important information to practicing clinicians using figures, images, tables, and algorithms in a most artful rendition. The contributors are practicing clinicians, and they have produced a clear and concise review of prostatic diseases. The format emphasizes figures and tables over text to accurately and quickly provide the pertinent thoughts regarding prostatic disease management for the busy clinician.

The 1990s were a time of dramatic change in the management of prostatic disease. Prior to these recent advances, men suffering from benign prostatic hyperplasia were routinely relegated to transurethral resection of the prostate or observation. There is now a complete array of therapeutic options for these patients, ranging from medical management to minimally invasive surgical techniques. This assortment of treatment options has generated a plethora of well-controlled randomized trials to investigate nearly every facet of management. The individuals who conducted many of these clinical trials, which so precisely inform us as to the efficacy of these treatments, are in many instances authors in this Atlas.

Prostate cancer management has likewise been an area of innovation and change in practice patterns. The emergence of brachytherapy with seed implantation of the prostate, new strategies for androgen manipulation of advanced prostatic cancer, and further attempts to identify effective chemotherapeutic agents are some of the advances in prostate cancer management seen in the past one to two decades.

When it comes to prostatic disease evaluation and management, this edition of *Atlas of the Prostate* has it all and does it all in a format that is easily comprehended and retained by the reader.

The authors deserve tremendous credit for their contribution to this *Atlas of the Prostate,* and the editors and illustrators at Current Medicine have worked diligently to provide this outstanding addition to the literature on prostatic diseases.

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CONTENTS

The Epidemiology and Pathophysiology of Benign Prostatic Hyperplasia

1

John D. McConnell

Although benign prostatic hyperplasia (BPH) is one of the most common disease processes affecting the aging man, surprisingly little is known about its pathophysiology [1]. Despite intense research efforts in the past four to five decades to find the underlying cause of prostatic growth in older men, cause and effect relationships have not been established. Previously held notions that the clinical symptoms of BPH (prostatism) are simply due to a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of the symptoms are caused by obstruction-induced detrusor dysfunction. Moreover, obstruction may induce a variety of neural alterations in the bladder and prostate that contribute to symptomatology. Undoubtedly, the constellation of cellular pathologies that give rise to the symptoms of BPH will be far more complex than we currently realize. Only by revealing these complexities, however, will we be able to successfully design alternative strategies to treat, and possibly prevent, BPH.

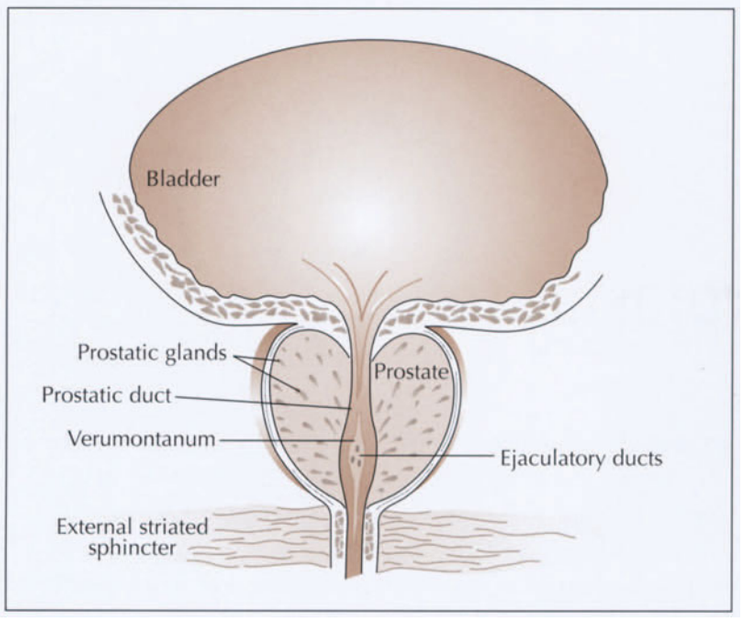

FIGURE 1-1. Anatomy. Benign prostatic hyperplasia (BPH) begins as a histologic disease in the fifth or sixth decade of life. McNeal's [2] careful anatomic studies suggest that the hyperplasia starts first with mesenchymal nodule formation in the periurethral area of the prostate. This is followed by the development of epithelial nodules in the transition zone of the prostate. Outward growth of the prostate is somewhat contained by the presence of a fibrous capsule [1]. Because of the restraining influence of the capsule and the plastic elements present in the tissue, ongoing growth tends to increase urethral resistance. The only other animal species known to develop BPH, the dog, does not develop significant urinary difficulty. The canine prostate, which lacks a capsule, tends to grow away from the urethra, producing rectal obstruction.

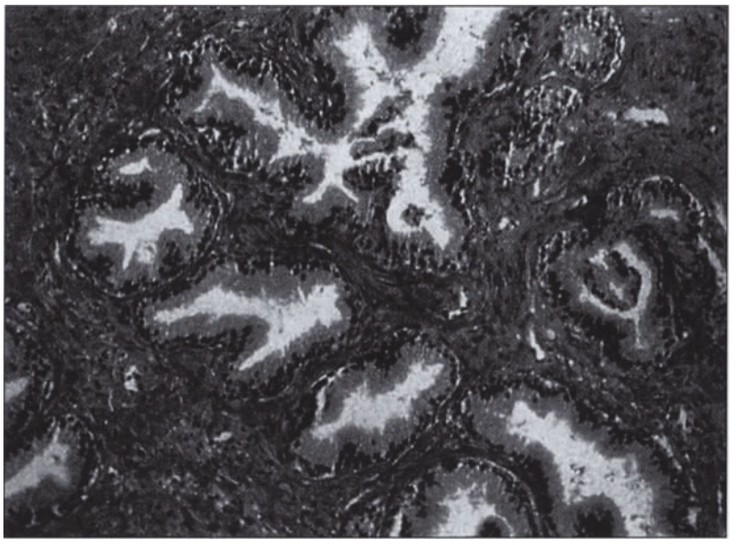

FIGURE 1-2. Histology of benign prostatic hyperplasia (BPH). Histologically, BPH is characterized by a combination of epithelial and stromal hyperplasia of varying degrees. The majority of patients demonstrate a fibromyoadenomatosis pattern of hyperplasia [2]. However, the degree of stromal versus epithelial hyperplasia can be quite variable, with some patients demonstrating almost a pure smooth muscle proliferation pattern. Despite the increase in prostate epithelial mass, prostatic secretions actually decline with age, probably secondary to compressive ductal obstruction [1].

Definitions Useful for Increased Precision of Diagnosis and Treatment

Term	*Definition*
LUTS	Lower urinary tract *symptoms*
BPE	Benign prostatic *enlargement*
BOO	Bladder outlet *obstruction*
BPH	Benign prostatic *hyperplasia*

FIGURE 1-3. Definitions useful for increased precision of diagnosis and treatment. Patients seek medical attention because of bothersome lower urinary tract symptoms (LUTS) [3]. Although 80% of men develop the histologic disease of benign prostatic hyperplasia (BPH) by the time they reach the eighth decade of life, only a subset of those men will develop bothersome urinary symptoms [4]. Although histologic hyperplasia is almost universal, not all men develop significant prostatic enlargement. Moreover, the degree of bladder outlet obstruction is only indirectly influenced by prostatic size. When studying the epidemiology and clinical course of BPH, it is important to precisely arrive at a *case definition* [4]. Are we studying enlargement, symptoms, obstruction, or a definition that combines all aspects of the disease? Moreover, the major benefit of treatment approaches should be defined according to these definitions. Does a given treatment target enlargement or symptoms?

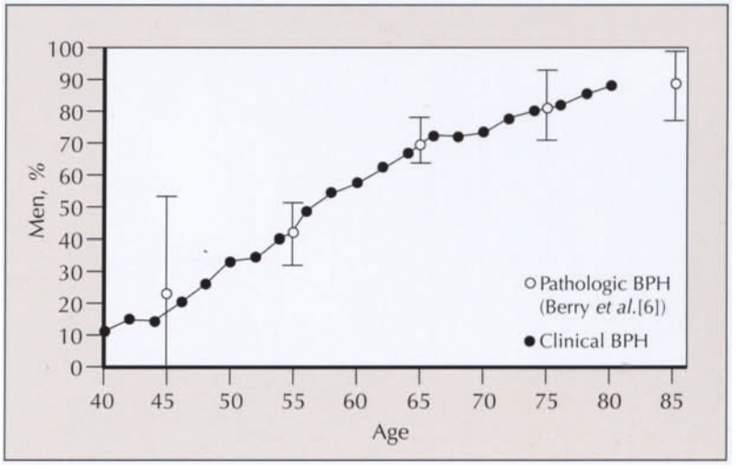

FIGURE 1-4. Clinical progression of benign prostatic hyperplasia (BPH). Although the correlation between prostatic size and symptom severity is poor in individual patients, there is an interdependence that becomes apparent in analysis of large cohorts of men. Guess *et al.* [5] from the Baltimore Longitudinal Study of Aging (BLSA) demonstrated that a clinical definition of BPH (defined by symptoms and evidence of prostate enlargement on digital rectal examination) correlated closely with the histologic evidence of BPH at each decade of year (defined by the Hopkins autopsy study performed by Berry *et al.* [6].) Eighty percent of men in the BLSA study developed clinical evidence of BPH by the time they reached the eighth decade of life. Approximately 25% of these men have significant loss of quality of life and may be appropriate candidates for medical or surgical intervention [7].

Definitions of Benign Prostatic Hyperplasia Progression

Symptomatic deterioration
Increasing bothersomeness
Urinary retention
Progression to surgery
Renal insufficiency

FIGURE 1-5. Definitions of benign prostatic hyperplasia (BPH) progression. The time course and severity of BPH in an individual patient is variable [7,8]. Moreover, the probability of specific adverse outcomes is variable. The most common adverse outcome is the development of bothersome urinary symptoms. In addition, a patient with a stable level of symptoms may develop increasing bothersomeness, *ie*, simply growing tired of the same level of symptoms. One to two percent of patients per year with significant prostatic enlargement may develop acute urinary retention [9]. Approximately one half of these cases will be precipitated by anesthesia or α-sympathomimetic medications, *eg*, decongestants. Because of symptom progression of the development of urinary retention, 10% to 25% of patients ultimately require BPH-related surgery [9]. The most unlikely complications are the development of obstruction-related renal insufficiency and recurrent urinary tract infection. "Silent prostatism" (*ie*, obstructive uropathy in the absence of symptoms) is an extremely rare outcome.

Biologic Progression of Benign Prostatic Hyperplasia

Prostate growth
Obstruction-related bladder dysfunction
Age-related bladder dysfunction
Medical comorbidity (diabetes, Parkinson's disease, stroke)

FIGURE 1-6. Biologic progression of benign prostatic hyperplasia (BPH). The underlying biologic causes for clinical progression are complex. Ongoing growth of the prostate undoubtedly contributes significantly to clinical progression. However, nonprostatic causes are also important. Obstruction produces significant changes in bladder function, which may continue after relief of the obstruction [10]. Obstruction-related bladder dysfunction may also continue in patients who have partial relief of symptoms from medical therapy, but incomplete relief of obstruction. Often overlooked is the importance of age-related declines in bladder function, which occur in both men and women. The density of nerve fibers in the bladder decreases with age, and extracellular matrix (ECM) formation (*eg*, collagen) increases [11]. Frequency, urgency, and incomplete emptying (often considered to be symptoms of prostatic enlargement) are also seen in women. Lastly, a patient may have symptomatic progression because of the development of medical comorbidities (*eg*, diabetes, Parkinson's disease, or stroke), which adversely affect bladder function [1].

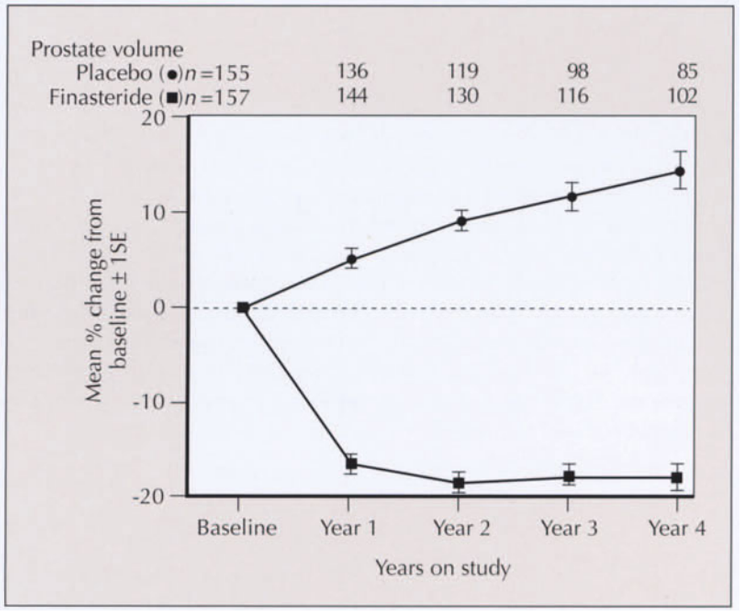

FIGURE 1-7. Changes in prostate volume over time according to the results of the Proscar Long-term Efficacy and Safety Study (PLESS). Once the benign prostatic hyperplasia (BPH) process has begun, the prostate continues to grow in 80% to 90% of patients. PLESS, the longest term prospective trial to date, demonstrated a 2- to 3-cc increase in prostatic volume per year [9]. Community-based studies demonstrate a slower prostate growth rate of approximately 1- to 2-cc per year [12]. This finding suggests that men with significant prostate enlargement (*eg*, those enrolled in PLESS) may have more rapid rates of prostatic growth. Whether this is genetically determined or a result of feedback influences on prostate growth (*eg*, increased growth factor production in larger prostates leading to even more growth) is uncertain.

Controversy Regarding Prostate Size

Prostate size does not correlate with symptom severity
Weak correlation with urodynamic obstruction
Community-based studies demonstrate correlation between prostate size and risk

FIGURE 1-8. Controversy regarding prostate size and future risk. Until recently, it was controversial whether ongoing growth of the prostate contributed significantly to the pathophysiology of lower urinary tract symptoms. This school of thought arose from clinical studies that demonstrated a very poor correlation between prostate size and symptom severity or the degree of urodynamic obstruction [13]. However, Jacobsen *et al.* [12] demonstrated in a community-based epidemiologic study that prostate size predicts the future risk of acute urinary retention and the need for prostate surgery.

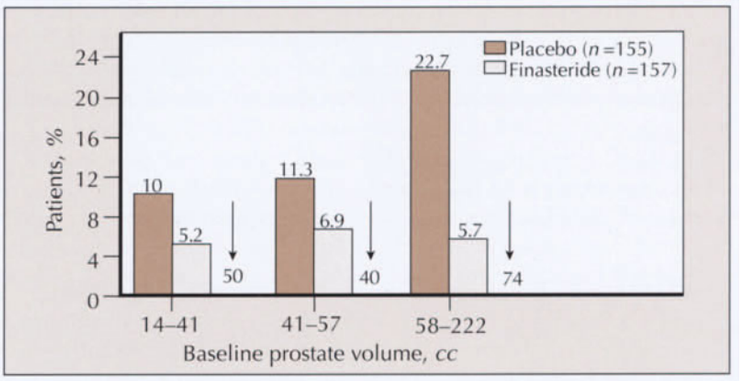

FIGURE 1-9. Relationship between prostate size and the risk of benign prostatic hyperplasia (BPH) clinical progression. The Proscar Long-term Efficacy and Safety Study (PLESS) demonstrated a very clear relationship between prostate size and the risk of BPH clinical progression [9]. Men with prostate volumes greater than 58 cc were two times more likely to develop acute urinary retention or need BPH-related surgery than men with prostate volumes less than 40 cc. The androgen dependence of BPH progression was demonstrated by the ability of the 5α-reductase inhibitor finasteride to reduce the risk of future surgery or acute retention in men who had significant enlargement. Although these data strongly suggest that ongoing growth of the prostate is an important component of the disease process, the factors that contribute to symptom severity (bladder dysfunction and patient perception of difficulty) make it difficult to establish a correlation between symptoms and prostate size. In contrast, adverse outcomes, such as acute urinary retention, are clearly influenced by prostate size.

Pathophysiology of Benign Prostatic Hyperplasia

Prostate growth
Increased urethral resistance
Decreased force of stream and intermittency, primarily obstructive symptoms
Detrusor response to maintain flow
Frequency, urgency, and nocturia, primarily detrusor (failure to store) symptoms

FIGURE 1-10. Pathophysiology of benign prostatic hyperplasia (BPH). The classic view of BPH pathophysiology is undoubtedly too simplistic. Nevertheless, this model still provides a rational framework for the diagnosis and treatment of the disease. Ongoing growth of the prostate leads to increases in urethral resistance. The symptoms of decreased force of stream and intermittency are primarily related to the increase in urethral resistance. The bladder responds to increased urethral resistance initially with smooth muscle hypertrophy, which permits the bladder to increase voiding pressures to maintain flow. However, the increased pressure occurs at the expense of bladder storage function, with symptoms such as frequency, urgency, and nocturia becoming the predominant aspects of the disease. This simple model ignores the important contribution of aging and central nervous system dysfunction, which may occur independent of prostatic obstruction.

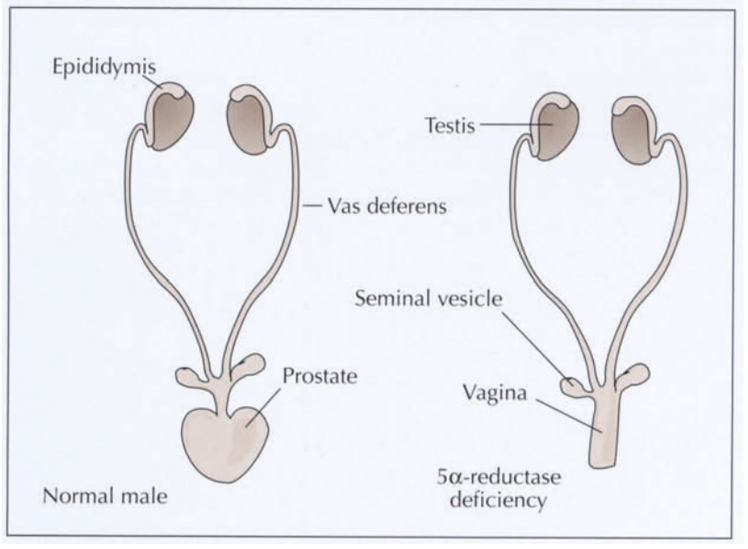

FIGURE 1-11. The syndrome of 5α-reductase deficiency. The development of benign prostatic hyperplasia requires testicular androgens and aging [14]. The importance of androgens in prostate development is demonstrated by the syndrome of 5α-reductase deficiency. Normally, the prostate develops from the urogenital sinus, under the influence of dihydrotestosterone (DHT), which is formed from testosterone by the enzyme 5α-reductase type 2. When 5α-reductase type 2 is genetically deficient, the prostate does not develop. The wolffian duct structures, which require testosterone for development, form normally. DHT is not only important for prostatic development, but is also required for growth of the prostate during puberty and adulthood.

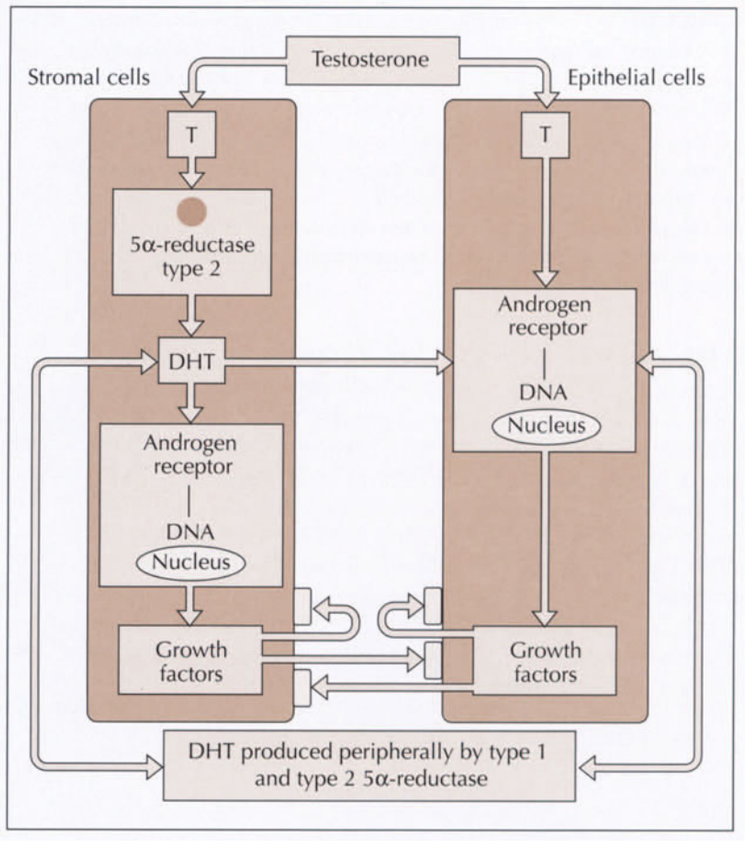

FIGURE 1-12. Effects of testosterone on stromal and epithelial cells. The primary androgen reaching the prostate is testosterone, which is produced in the Leydig cells of the testis [14]. Testosterone may have a direct effect on the epithelial cell of the prostate, but 90% of intraprostatic testosterone is converted to dihydrotestosterone (DHT) within the stromal cell by type 2 5α-reductase. The DHT made in the stromal cell then acts on the adjacent epithelial cells through a paracrine mechanism. Alternatively, DHT made in the stromal cell may promote the expression of growth factors that work secondarily on the epithelial cell. Significant levels of DHT are made in the skin and liver by type 1 and type 2 5α-reductase isoenzymes [15]. It is uncertain whether DHT made in the periphery can act on the prostate in a true endocrine fashion.

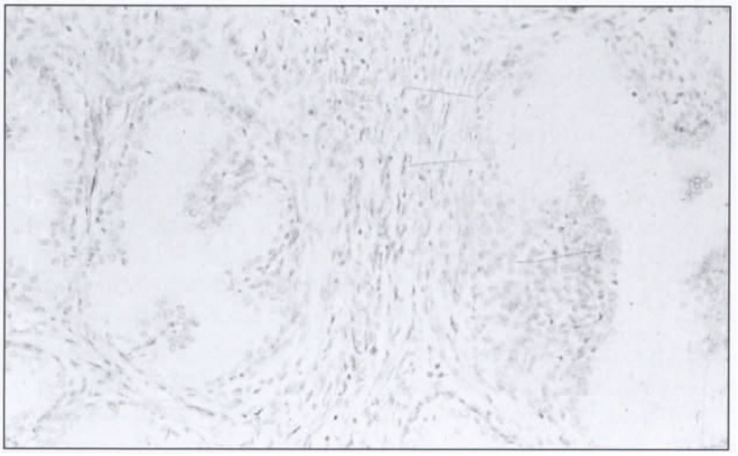

FIGURE 1-13. ***(See Color Plate)*** Prostate tissue sample. As demonstrated in this section stained with an antibody against type 2 5α-reductase, the enzyme is clearly located in the prostatic stroma [16,17]. Stroma immediately adjacent to hyperplastic epithelial nodules appear to express slightly higher levels of 5α-reductase, which may promote locally increased production of dihydrotestosterone (DHT). However, it appears that DHT production is necessary for the development of benign prostatic hyperplasia, but not causative. Analysis of prostate tissue samples from men with BPH demonstrates no higher levels of DHT [18].

The 5α-Reductase Isozymes

	Type 1	*Type 2*
pH optima	6.0–8.5	5.0
Ki finasteride	230–300 nM	3 to 5 nM
Activity in deficiency state	Normal	Reduced or abnormal
Homology, %	50	50

FIGURE 1-14. The 5α-reductase isoenzymes. Two 5α-reductase isoenzymes have been reported to date [15]. The type 2 isoenzyme is the predominant, if not exclusive, isoenzyme found in the prostate. It is the enzyme that is mutated in the 5α-reductase deficiency state and that is exquisitely sensitive to inhibition by finasteride. Type 1 5α-reductase is expressed mainly in skin and liver; it is not inhibited by finasteride. Pharmaceutical companies have developed drugs that inhibit both type 1 and type 2 5α-reductase isoenzymes. However, because the type 2 enzyme is the predominant form in the prostate, it is unclear whether combined inhibitors will have additional efficacy in the treatment of benign prostatic hyperplasia.

Stromal Hyperplasia in Benign Prostatic Hyperplasia

Primitive mesenchymal nodules differentiated into stromal nodules containing mature smooth muscle cells
Ongoing growth of the prostate assumes ongoing stromal hyperplasia

FIGURE 1-15. Stromal hyperplasia in benign prostatic hyperplasia (BPH). Stromal hyperplasia is an important component of the disease process. Indeed, the normal ratio between stroma and epithelium in the prostate of a 20-year-old man is approximately 2:1. In prostate tissue obtained by transurethral resection, stromal-to-epithelial ratios are more commonly 5:1 [19]. Although the ratio between stroma and epithelium is variable, with more significant epithelial hyperplasia in larger prostates, it is clear that stromal proliferation is an important part of the disease process. Ongoing growth of the prostate cannot occur unless there is ongoing stromal hyperplasia.

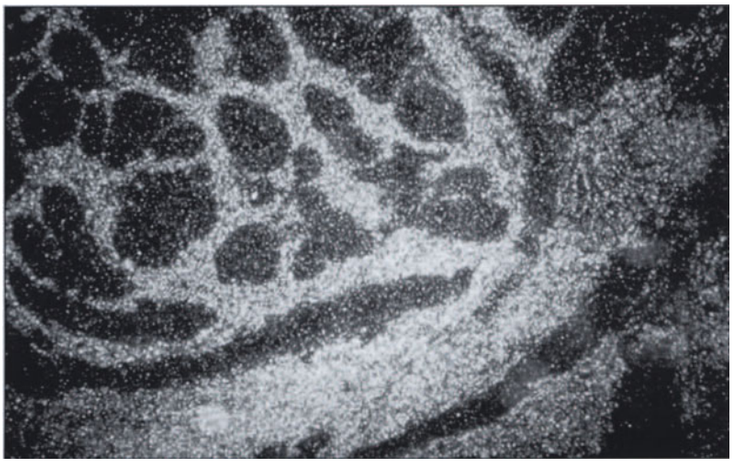

FIGURE 1-16. Prostatic stroma. A major component of the prostatic stroma is haphazardly arranged smooth muscle. This section demonstrates an in situ hybridization of a benign prostatic hyperplasia (BPH) nodule utilizing a probe that identifies the messenger RNA of a specific smooth muscle marker (myosin heavy chain). The dense bands of smooth muscle surrounding epithelial nodules, as well as significant smooth muscle between individual glands, is evident. Smooth muscle proliferation in other disease states (*eg*, atherosclerosis) is known to be regulated by growth factors. Some growth factors (*eg*, transforming growth factor-β) act as a "brake" on stromal cell proliferation [20]. Other growth factors (*eg*, basic fibroblast growth factor) produce stromal cell proliferation [21]. The role of growth factors in BPH remains to be elucidated.

Composition of Prostatic Stroma

Smooth muscle
Fibroblasts
Extracellular matrix
Vascular structures
Neural elements
Immune cells

FIGURE 1-17. Composition of prostatic stroma. Prostatic stroma has a complex composition. In addition to smooth muscle, there is significant volume of fibroblasts, extracellular matrix (collagen and elastin), vascular structures, neural elements, and immune cells. Indeed, morphometric measurements have demonstrated that the extracellular matrix on a volume basis is the most abundant component of the hyperplastic prostate [19]. Forty to fifty percent of benign prostatic hyperplasia (BPH) biopsy or surgical specimens demonstrate significant chronic and inflammatory infiltration. Because lymphocytes are known to elaborate cytokines that produce smooth muscle contraction and cell proliferation, the immune cells may well be part of the pathophysiology of BPH.

Force Generation of Prostate Tissue

A determinant of urethral resistance
Components of force include:
Active (smooth muscle contraction)
Passive (series elastic elements)

FIGURE 1-18. Force generation of prostate tissue. The importance of the extracellular matrix in benign prostatic hyperplasia cannot be overestimated. Active contraction of the smooth muscle elements in the prostate (often referred to as the dynamic component of the disease) certainly influence urethral resistance. However, it has been estimated that only 50% of urethral resistance is determined by active smooth muscle contraction. The remainder of urethral resistance is determined by the so-called passive series elastic elements in the prostate [1]. These forces are caused by the intrinsic "rubberband" nature of the collagen and elastic tissue in the gland. The clinical importance of these passive forces is illustrated by the effectiveness of transurethral incision of the prostate, where simple incision through the prostatic tissue and capsule relieves outflow resistance without any debulking of prostatic tissue. This also explains why α-blockade (which does not affect the passive forces) fails to relieve urodynamic obstruction.

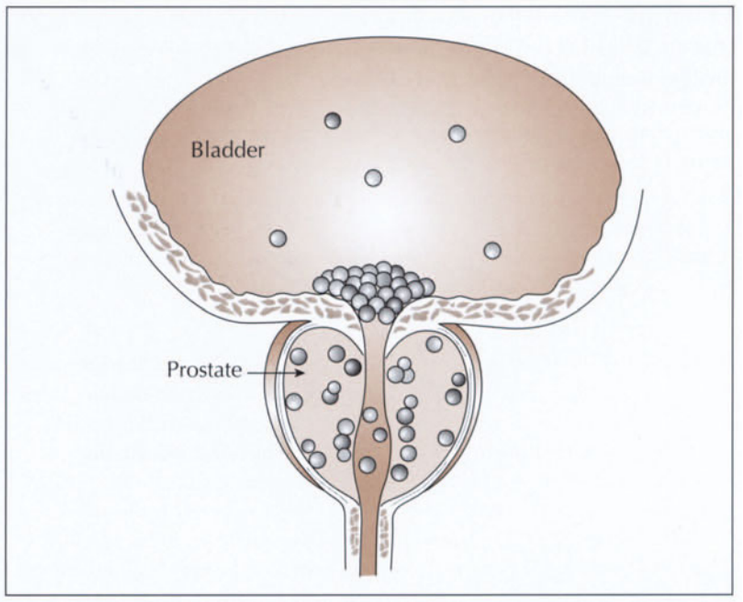

FIGURE 1-19. Distribution of α1 adrenoceptors in lower genitourinary tissues. The male lower urinary tract contains an abundance of α_{1a}-adrenoreceptors in the prostatic smooth muscle and bladder neck [22]. In contrast, the detrusor smooth muscle contains few, if any, α1 receptors. α-Adrenergic blockage, therefore, can produce selective relaxation of smooth muscle at the bladder outlet, without adversely affecting detrusor performance.

Active Force Generation in Prostate Smooth Muscle

Adrenergic neurotransmission
Purenergic neurotransmission
Endothelin
Nitric oxide inhibition
Cytokines

FIGURE 1-20. Active force generation of prostate smooth muscle. Although release of norepinephrine in adrenergic nerve terminals in the prostate is responsible for the majority of active smooth muscle contraction [23], other substances may modulate smooth muscle tone in the prostate. For example, endothelin, the most potent vasoconstrictor yet discovered, is present in fairly high levels in the prostate [24]. In addition, all the components of the nitric oxide pathway, which mediates smooth muscle relaxation, have been found in the prostate. As already mentioned, lymphocytes, commonly found in benign prostatic hyperplasia, may elaborate chemicals (cytokines) that produce smooth muscle contraction. It seems unlikely that adrenergic blockade will produce complete smooth muscle relaxation in the prostate. Some of the nonadrenergic pathways regulating smooth muscle contraction may be targeted for future drug development.

Aspects of the Adrenoreceptor Family

α_{1a} is the most abundant adrenoreceptor messenger RNA in the prostate (60% to 85%)
The presence of another receptor subtype with low affinity to prazosin, $\alpha_{1a'}$ is suggested

FIGURE 1-21. Aspects of the adrenoreceptor family of genes. This family encodes different receptor subtypes that vary in their tissue distribution. The most abundant adrenoreceptor messenger RNA in the prostate is the α_{1a} subtype [23]. The α_{1a} is clearly the subtype that mediates contraction of prostatic smooth muscle [22]. However, there are other adrenoceptor subtypes in the prostate and it is unclear whether the benefit of α-blocker therapy in benign prostatic hyperplasia resides purely with blockade of the α_{1a} receptor.

α-Receptors in the Nervous System

Facilitatory α1 receptors tonically active in both the sympathetic and somatic control of the lower urinary tract
Doxazosin may have an action at the spinal cord and ganglia level to reduce activity in the parasympathetic nerves going to the bladder
Concept of prostate-selective versus uroselective

FIGURE 1-22. α-Receptors in the nervous system. There is increasing evidence that α-receptors in the central nervous system may be important modulators of urinary function. Facilitory α1 receptors are active in both the sympathetic and parasympathetic modulation of the lower urinary tract. The symptom improvement seen with α-blocker therapy may partially depend on central nervous system affects. Thus, drugs that are specifically designed to be "prostate selective" may have less than therapeutic benefit. Doxazosin, for example, has been shown in an animal model to have clear effects on the spinal cord to reduce the activity of parasymmetric nerves going to the bladder [23,24].

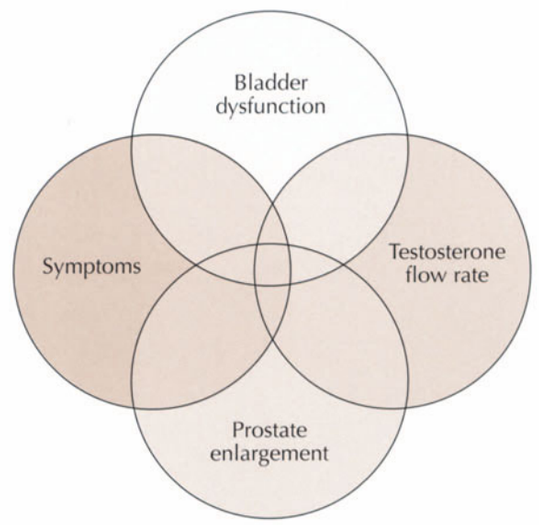

FIGURE 1-23. Interrelated factors in prostate enlargement. Although ongoing growth of the prostate is clearly a major component of progressive symptoms and declining flow rate, the contribution of the bladder cannot be ignored [1]. Bladder dysfunction, in fact, may occur independent of obstruction and produce symptoms that are identical to those seen with prostatic enlargement.

Detrusor Response to Obstruction

Detrusor instability
Impaired contractility
Increased extracellular matrix
Decreased compliance
Alteration in neural pathways and modulation

FIGURE 1-24. Detrusor response to obstruction. The bladder's response to obstruction is variable and incompletely defined. In animal models, bladder outlet obstruction initially leads to development of smooth muscle hypertrophy, which progresses over time to significant fibrosis [10]. Detrusor instability (uninhibited bladder contractions) occurs during this smooth muscle hypertrophy process, probably because of a disruption of coordinating signaling processes between individual smooth muscle cells. Paradoxically, instability is associated with impaired contractility. Increases in extracellular matrix (predominately collagen) become the predominant feature of the long-term obstructed bladder, ultimately leading to decreased compliance. There is also evidence that obstruction may lead to alteration of neural pathways in the sacral spinal cord, micturition center, and cerebral cortex [25].

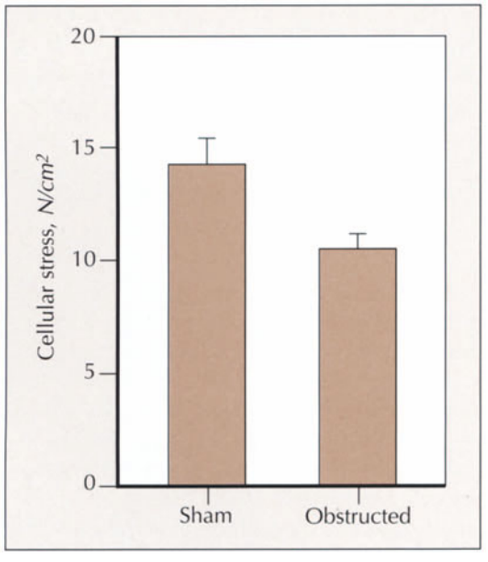

FIGURE 1-25. Cellular stress study results. In our research laboratories at the University of Texas Southwestern Medical Center, we demonstrated that bladder outlet obstruction in an animal model (rabbit) produces significant smooth muscle hypertrophy in a period of 2 to 3 weeks [26]. Overall, there is a two- to fourfold increase in muscle mass in the bladder. However, the amount of force that individual muscle cells can produce per cross-sectional area declines significantly.

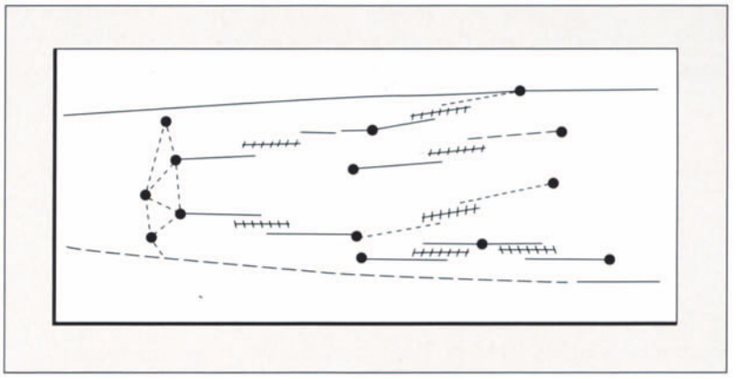

FIGURE 1-26. The complex array of thick and thin filaments inside individual smooth muscle cells. The thin filaments consist of actin cables that provide structural support for the cell. The thick filaments consist of the protein myosin, which when stimulated produces movement along the actin cables. The movement along adjacent actin filaments produces shortening of the smooth muscle cells and thus bladder emptying. Studies of hypertrophied smooth muscle demonstrate that although the cells enlarge significantly, they tend not to increase their level of contractile filaments proportionately [26]. Hypertrophied smooth muscle does not behave like hypertrophied skeletal muscle (*eg*, in response to weight training), in which the number of contractile filaments keeps pace with overall growth of the cell.

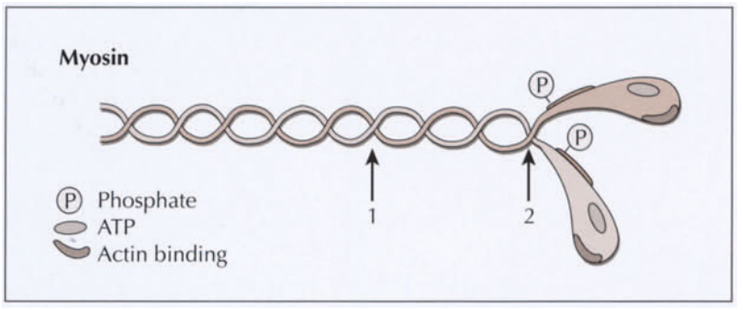

FIGURE 1-27. Structure of myosin. The protein responsible for contraction of muscular tissue is myosin. Myosin is a complex hexometric molecule that consists of two heavy chains and four light chains. The myosin heavy chains catalyze the hydrolysis of ATP, transforming the chemical energy of hydrolysis to the mechanical energy of myosin movement.

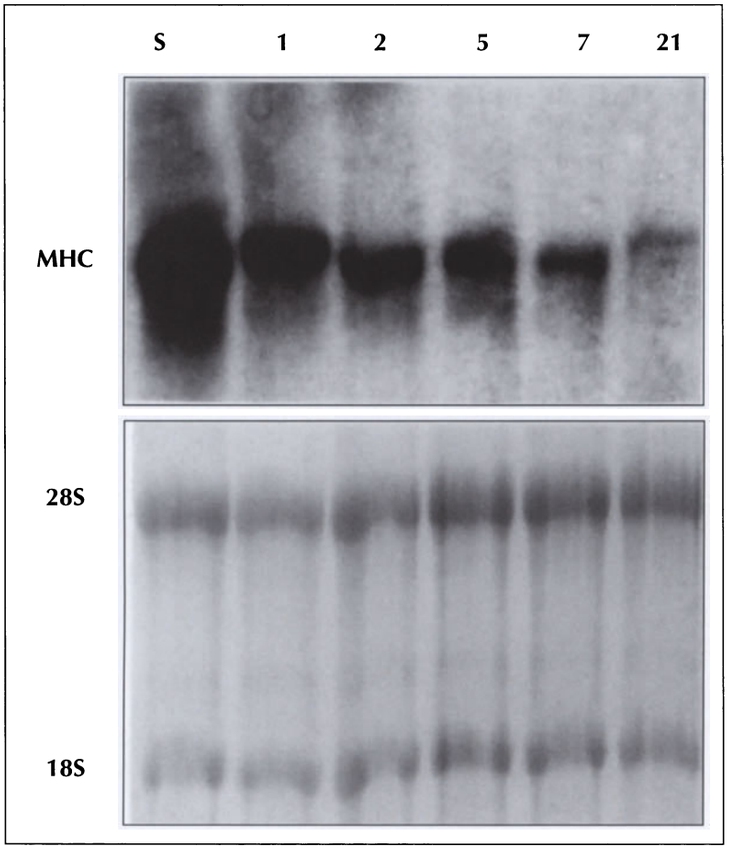

FIGURE 1-28. Northern blot analysis of bladder obstruction in an animal model. We demonstrated that smooth muscle hypertrophy is associated with a significant decline in major histocompatibility complex (MHC) expression [26]. The amount of messenger RNA for MHC is evident as the dark band in the *upper panel*. The column labeled "S" is analysis of messenger RNA from sham-operated animals demonstrating a very high level of MHC expression. After only 1 day of obstruction, however, there is a significant decline in MHC expression, and by 21 days it is difficult to detect. Total RNA within the cell (*lower panel*) remains stable. The smooth muscle cells develop a significant increase in proteins that structurally support the cell (*eg*, desmin) but do not produce contraction.

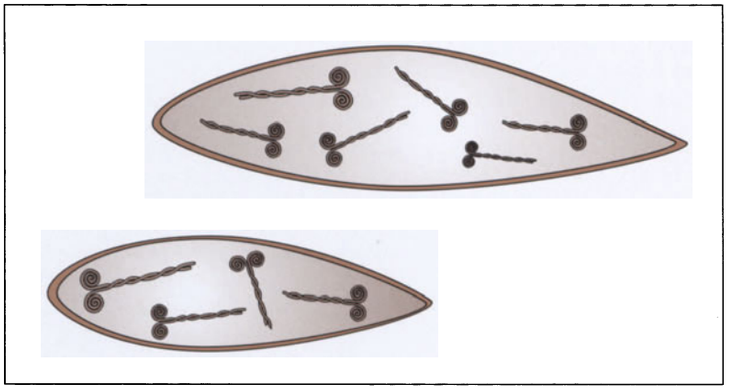

FIGURE 1-29. Obstruction-induced smooth muscle cell hypertrophy. This is not an entirely adaptive process. Although the cell enlarges significantly, the number of contractile elements present in the cell do not increase proportionally. The overall increase in bladder muscle mass seen with obstruction permits the generation of higher pressures, but the decreased number of contractile elements adversely influences the performance of the bladder, leading to impaired emptying.

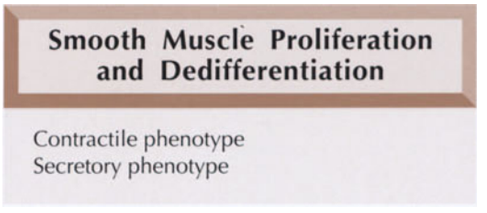

FIGURE 1-30. Smooth muscle proliferation and dedifferentiation. Another important attribute of smooth muscle hypertrophy is the conversion from a muscle cell predominantly responsible for contraction (contractile phenotype) to a less differentiated type of smooth muscle cell that becomes more of a secretory cell [26]. The smooth muscle secretory phenotype is characterized by both a decline in smooth muscle contractile proteins and a significant increase in extracellular matrix production (predominantly collagen).

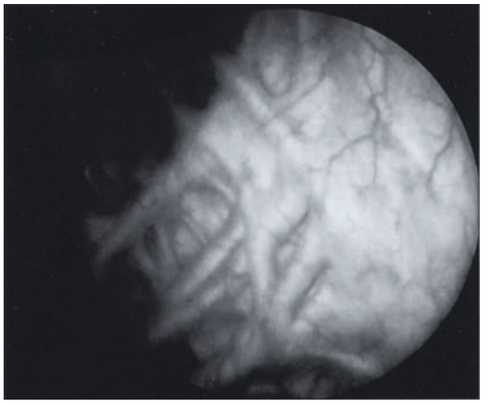

FIGURE 1-31. ***(See Color Plate)*** Endoscopic image of the obstructed bladder. The significant increase in collagen production seen in the obstructed bladder is responsible for the trabeculation seen endoscopically in men with bladder outlet obstruction. This is not the "rippling muscle" of an obstructed bladder, but rather a significant increase in extracellular matrix.

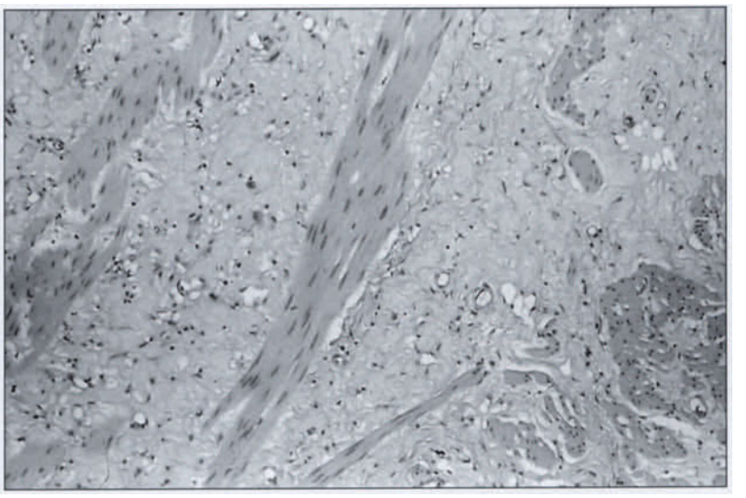

FIGURE 1-32. ***(See Color Plate)*** Biopsy specimen of a trabeculated bladder. This specimen demonstrates scarce smooth muscle fibers with a significant increase in collagen. This increase in extracellular matrix limits the compliance of the bladder, leading to higher pressures with bladder filling. Moreover, the collagen fibers limit shortening of adjacent smooth muscle cells. The increase in extracellular matrix in the bladder is the predominant cause of impaired emptying. Residual urine develops because the bladder wall cannot completely contract.

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Clinical Evaluation of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

2

Christopher E. Kelly & Philippe E. Zimmern

The practitioner should be adept at identifying those tests and procedures necessary to evaluate men with lower urinary tract symptoms (LUTS). Prior to any discussion on evaluation of LUTS, however, one must be aware of the changing terminology, which was born out of frustration with inadequate communication. The relatively new LUTS terminology was introduced by Abrams [1] to replace the old terms "prostatism," "clinical benign prostatic hypertrophy (BPH)," and "symptomatic BPH," because these latter terms implied that the prostate is responsible for all or most of the LUTS in men. Whereas it is well established that LUTS can be precipitated by benign prostatic enlargement (BPE) and bladder outlet obstruction (BOO), LUTS can also occur secondary to aging, neurologic diseases, and extravesical causes [2,3]. Similarly, the use of terms such as "irritative" and "obstructive" in the absence of supporting objective data was imprecise and confusing. For example, a man's irritative symptoms of urgency or frequency may result from high bladder volumes or detrusor overactivity secondary to BOO; conversely, obstructive symptoms such as weak force of stream and abdominal straining may result from detrusor hypocontractility and not from BOO. Similarly, the term BPH implies a histologic diagnosis, which should be reserved for known prostatic tissue pathology. Also, the International Consultation on BPH (IC BPH) recommended that the terms "BPE" and "BOO" be used when appropriate to increase accuracy of communication [4].

Benign prostatic enlargement associated with BOO is the principal cause of LUTS; however, some patients with BPE, regardless of their degree of prostatic enlargement, may not have LUTS and may not have urodynamically defined BOO [5]. Furthermore, other patients with urodynamically confirmed BOO may not have LUTS [6]. Although studies have shown that patients with BPE and no urodynamic evidence of BOO can have LUTS, it is not clear how BPE alone can induce LUTS. It has been proposed that increased or altered neural afferentation due to BPE may be responsible for the symptoms in this group [7,8]. LUTS can also be secondary to pharmacologic agents that may directly or indirectly affect lower urinary tract function [9]. These agents include antihistaminics, diuretics, calcium channel blockers, tricyclic compounds, sedatives, and cold remedies coupled with α-adrenergic agonists.

Lower urinary tract symptoms should be assessed using a multidimensional approach that takes into account all participating factors before therapies that are primarily directed at BOO are implemented.

In 2000, the IC BPH guidelines set forth recommendations to physicians evaluating LUTS. These guidelines include a detailed medical history, a

genitourinary examination including a digital rectal examination (DRE), and a prostatic-specific antigen (PSA) test. Optional studies included the urinalysis and serum creatinine [10].

The medical history should search for any comorbid diseases and include a detailed pharmacologic history and a voiding diary. Also recommended is the use of patient symptom questionnaires. The most widely used and most intensively studied lower urinary tract symptom questionnaire is the International Prostate Symptom Score (IPSS), an adopted version of the American Urological Association Symptom Score [10]. Another "popular" symptom-measuring instrument is the ICS-BPH Study questionnaire [11]. Measuring voiding symptoms allows the physician to ascertain symptom severity, may uncover symptoms not brought up during the interview, and helps monitor symptoms on therapy. Questionnaires cannot establish the diagnosis of BPE, nor can they screen for BPE; in fact, some of the highest scores are generated by women with LUTS [12,13]. Although controversy continues as to which questionnaire measuring symptom severity is superior, more attention is now given to questionnaires measuring bothersomeness or quality of life indices.

The physical examination should evaluate for the presence or absence of a distended bladder, excoriation of the genitals secondary to urinary incontinence, evidence of urethral discharge, and genital abnormalities (*eg*, phimosis or meatal stenosis). A focused neurourologic examination, including assessment of the sacral cord reflexes (anal sphincter tone and bulbocavernosus reflex), and an assessment of motor and sensory functions of the lower extremities is also necessary.

Digital rectal examination has traditionally been used to evaluate prostatic size, consistency, shape, symmetry, tenderness and induration suggestive of prostate cancer. However, DRE is only moderately effective in estimating prostatic size when compared with transrectal ultrasound or MRI [14]. It should also be noted that in population-based studies, prostatic size did not correlate with the severity of LUTS [15].

Laboratory investigations considered standard by most national guidelines are the urinalysis and serum creatinine, which can be used to assess for urinary tract infections and renal function, respectively [1]. Other tests (*eg*, urinary cytology) may be used to screen for carcinoma in situ of the urothelium. PSA measurement is recommended by the IC BPH and other national guidelines in the initial evaluation of LUTS. However, the clinician should take into account the patient's age, life expectancy, and intent to treat. For example, a life expectancy of more than 10 years and a plan to treat prostate cancer if it is diagnosed is required by some guideline panels, including the IC BPH [16].

Endoscopic evaluation may be helpful in the clinical evaluation of LUTS. Cystourethroscopy may exclude causes of LUTS other than BPE, such as urethral stricture, bladder cancer, cystitis (infectious or radiation induced), and bladder stones. Bladder trabeculations have recently been shown to correlate significantly with urodynamically proven BOO and detrusor overactivity. However, 11% of patients with no trabeculations were found to be obstructed, whereas 8% with severe trabeculations had no obstruction [17,18]. Because endoscopic identification of a large median lobe may influence therapeutic decisions, cystoscopy is encouraged in patients with BOO seeking minimally invasive therapies.

Urinary flowmetry, although not considered standard by the IC BPH, can serve as a noninvasive screening test for selecting patients who should undergo more sophisticated urodynamic studies. This test, however, has several limitations. First, peak flow rates (Q_{max}) less than 15 mL/s do not necessarily differentiate between obstruction and detrusor impairment. Additionally, the peak flow rate (Q_{max}) can be highly variable among individual sequential voids [19] and does not correlate with the degree of obstruction. Lastly, a normal flow does not exclude obstruction [4].

The predictive role of postvoid residual (PVR) measurement is poor. A large residual urine can be secondary to detrusor failure or a direct result of BOO [20]. A high PVR, although unable to differentiate between obstruction and bladder decompensation, might predict a slightly higher failure rate with a "watchful waiting" strategy. Threshold values have been poorly defined. However, very high PVR values (> 300 mL) may increase the risk of upper tract dilation and renal failure [21].

Urodynamic evaluation is the gold standard for determining the true etiology of LUTS. Filling cystometrogram can detect the presence of detrusor overactivity, compliance changes, or reduction in maximum bladder capacity. Also, combined voiding pressure with flow studies can help distinguish between obstruction and impaired detrusor contractility or hypocontractility. Although not required for all patients, multichannel urodynamic evaluation is recommended for the following patients:

- Those in whom a diagnosis is difficult to infer from history, physical examination, and simple tests
- Those with a complex history of multiple prior surgeries
- Those with documented or suspected neurologic disease (*eg*, multiple sclerosis, spinal stenosis, parkinsonism, diabetes, stroke, chronic alcoholism, myelo- or autonomic neuropathies)
- Those in whom empiric treatments such as pharmacotherapy and biofeedback fail
- When irreversible or potentially morbid treatments are planned
- When results from uroflowmetry or PVR are grossly abnormal
- In young patients in whom underlying voiding dysfunction more so than BPE or BOO may be associated with LUTS [22]

Imaging of the urinary tract (videourodynamics or voiding cystourethrography) is sometimes helpful to diagnose the site of obstruction when BOO is suspected. For example, radiographic imaging may help locate the true location of obstruction in a patient with a prior history of failed lower urinary tract surgery. Transrectal ultrasound of the prostate (TRUS) can accurately assess prostate

volume and guide surgical decisions. Symptomatic patients with BPE in excess of 75cm^3 might be considered for open prostatectomy, while those with smaller glands may be offered more minimally invasive outflow-relieving procedures. Imaging of the upper urinary tract is very selectively recommended (men with a history of urinary tract infection, urolithiasis, hematuria, or renal insufficiency) [16]. In summary, the clinician must judiciously select appropriate methods of evaluation for successful management of elderly men with LUTS. Diagnosis before rather than after empiric treatment can avoid morbidity and is likely more cost-effective in the long run.

THE RELATIONSHIPS AMONG LOWER URINARY TRACT SYMPTOMS, BENIGN PROSTATIC ENLARGEMENT, AND BLADDER OUTLET OBSTRUCTION

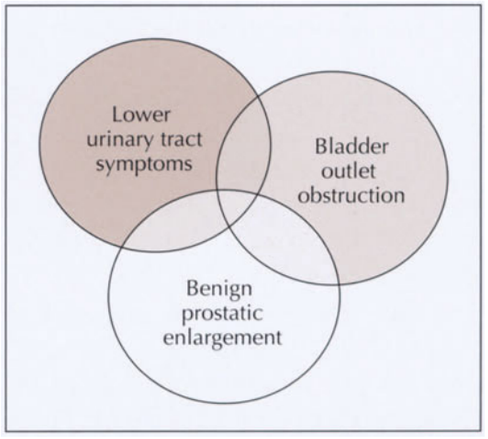

FIGURE 2-1. The interrelationships among lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE), and bladder outlet obstruction (BOO). These interrelationships can be complex [23]. As this Venn diagram shows, patients with BPE can have symptoms with or without BOO [24]. Furthermore, some patients with LUTS do not have BOO [25]. Other prostatic diseases, such as prostatitis or prostatic carcinoma, can lead to LUTS. Conversely, varying degrees of BOO have been detected in asymptomatic elderly men [6].

Although BPE without detectable BOO could produce LUTS via increased or altered afferent neural input [7], no large-scale studies have supported this hypothesis.

A. Causes of Urologic Lower Urinary Tract Symptoms

- Ureter
  - Acute distal ureteral irritation
    - Secondary to calculi or stent
- Bladder
  - Increased postvoid residual urine
    - From bladder outlet obstruction
    - From detrusor hypo- or areflexia
  - Involuntary detrusor contraction
    - Detrusor instability
    - Detrusor hyperreflexia
  - Intrinsic bladder wall disorder
    - Poor compliance
  - Bacterial cystitis
  - Interstitial cystitis
  - Trigonitis
  - Bladder aging
  - Bladder neoplasm
- Prostate
  - Benign prostatic enlargement
  - Prostate cancer
  - Prostatitis
- Urethra
  - Urethritis
  - Stricture

FIGURE 2-2. Urologic (**A**) and nonurologic

(*Continued on next page*)

B. Nonurologic Causes of Lower Urinary Tract Symptoms

- Excessive fluid intake
  - Learned behavior
  - Drug-induced polydipsia
    - Anticholinergics
    - Chlorpromazine
  - Psychogenic polydipsia
  - Hypothalamic disease
- Inadequate tubular reabsorption of water
  - Diabetes insipidus
    - Central
    - Nephrogenic
- Altered renal absorption of solutes
  - Glucose (diabetes mellitus)
  - Mannitol
  - Diuretics
- Sleep disorders
- Excess fluid mobilization when supine (*eg*, CHF)
- Pelvic floor muscle spasm
- CNS disorders
  - Multiple sclerosis
  - Parkinson's disease
  - Cerebral vascular accident
  - Trauma
- PNS disorders
  - Trauma
    - Iatrogenic (*eg*, after abdominal perineal resection)
    - Noniatrogenic
  - Infection
    - Herpes zoster
- Drugs
  - Inhibiting bladder contractility
    - Antihistamines
    - Antimuscarinics
    - β-antagonists
    - Psychotropic medications
  - Increasing outlet resistance
    - Adrenergic agonists
    - Imipramine
  - Increasing renal blood flow
    - Caffeine

FIGURE 2-2. *(Continued)* (**B**) causes of lower urinary tract symptoms (LUTS). LUTS can be produced by several factors that may or may not be primarily urologic in origin. CHF—congestive heart failure; CNS—central nervous system; PNS—peripheral nervous system.

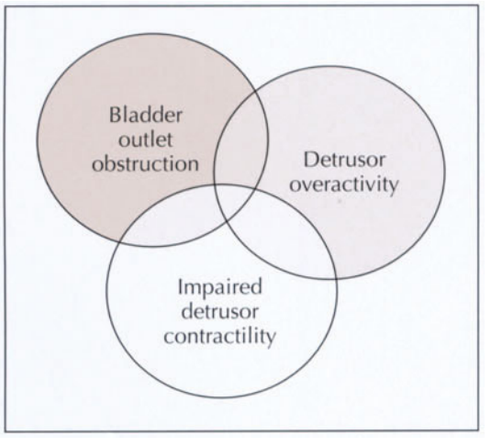

FIGURE 2-3. Functional abnormalities associated with benign prostatic enlargement (BPE). These include bladder outlet obstruction (BOO), detrusor overactivity (DO), and impaired detrusor contractility (IC). A combination of BOO, DO, and IC may coexist. Conversely, prostatic enlargement presumed to be caused by benign prostatic hypertrophy can sometimes be asymptomatic and manifest no urodynamic abnormalities.

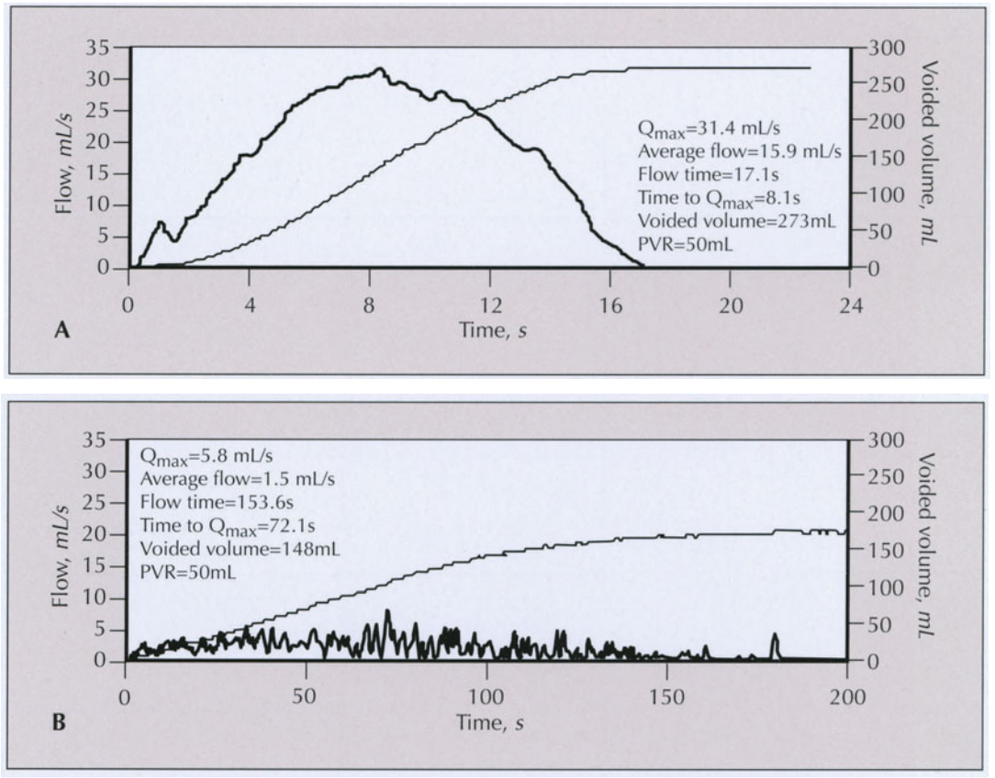

FIGURE 2-4. Uroflowmetry. Uroflowmetry is a simple, noninvasive urodynamic test that can be an invaluable screening tool for identifying those patients who require more extensive urodynamic evaluation. Thus, a patient with a low urinary flow rate will need further testing to discriminate between poor detrusor contractility and bladder outlet obstruction [26]. Various types of abnormal voiding patterns can be recognized from uroflowmetry parameters, and from the flow curve. Note that many studies report the maximum urinary flow rate (Q_{max}) as a measure of response to treatment. However, the dependence of Q_{max} on age and bladder volume (>150 mL) should not be overlooked in the final analysis. **A,** A normal urinary flow pattern is characterized by a bell-shaped curve with high Q_{max}. Note the short micturition time and the volume voided. Voided volumes less than 150 mL make uroflowmetry interpretation difficult. **B**, Abnormal uroflowmetry is characterized by a low maximum flow rate and a prolonged duration. Several flow patterns have been described that typify "obstructive flow," detrusor impairment, Valsalva voiding, and super-flow [27]. Uroflowmetry can alert the clinician when voiding is abnormal, thus prompting the recommendation for a pressure-flow study. PVR—postvoid residual.

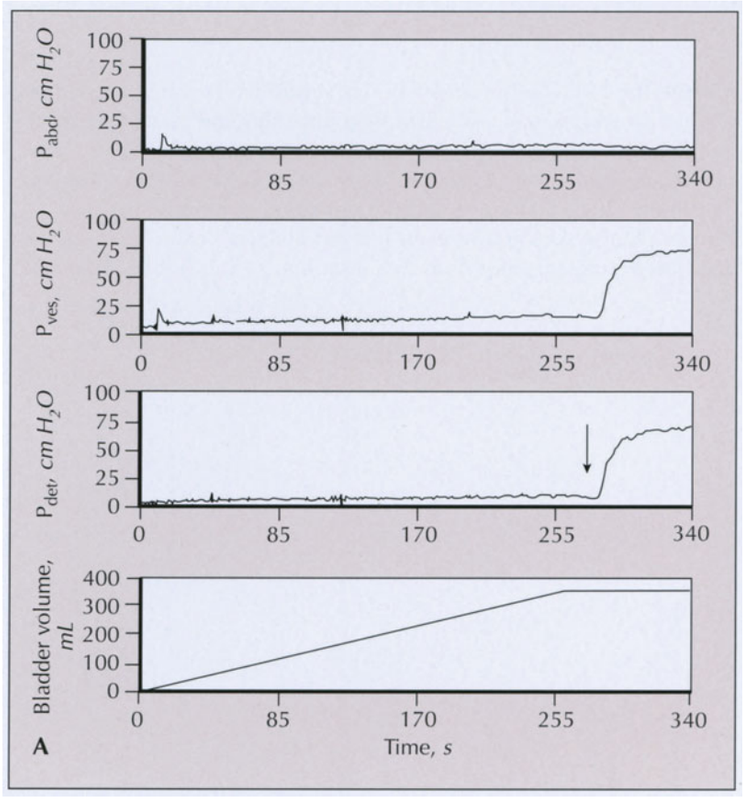

FIGURE 2-5. Cystometry. The multichannel cystometrogram (CMG) uses simultaneous pressure transducer catheters in the bladder (P_{ves}) and in the rectum (P_{abd}). The true bladder pressure (P_{det}) ($P_{det} = P_{ves}-P_{abd}$) is a mathematical derivative obtained from subtracting the abdominal pressure from the total pressure measured within the bladder.

A filling CMG provides objective data on bladder filling, desire to void, detrusor capacity, and detrusor compliance. It is particularly helpful when the patient's symptoms are reproduced during the test. Therefore, it is imperative that the clinician be highly observant of the patient's experience during the study. Also, several points can help to avoid pitfalls in interpretation. Rapid filling can artifactually cause detrusor overactivity. Thus, an involuntary detrusor contraction corresponds to a symptomatic involuntary intravesical pressure rise, which the patient cannot actively inhibit. One should also remember that spontaneous rectal contractions can affect P_{abd} and result in a falsely reduced detrusor pressure. Lastly, detrusor compliance, measured by dividing the change in the bladder volume to the rise in detrusor pressure, is dependent on filling rate and volume [28].

A, A normal filling CMG in an adult man is characterized by a bladder capacity of 350 to 500 mL with low detrusor pressure and absence of involuntary contractions. In this 64-year-old asymptomatic man, bladder capacity was 360 mL with a bladder compliance of 60 mL/cm H_2O. The *arrow* indicates the onset of a voluntary bladder contraction.

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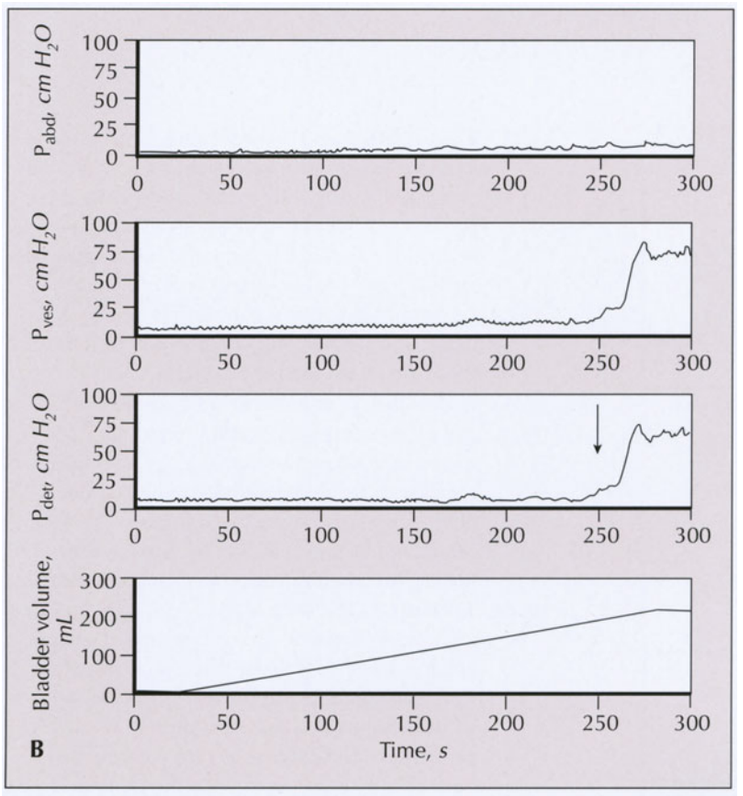

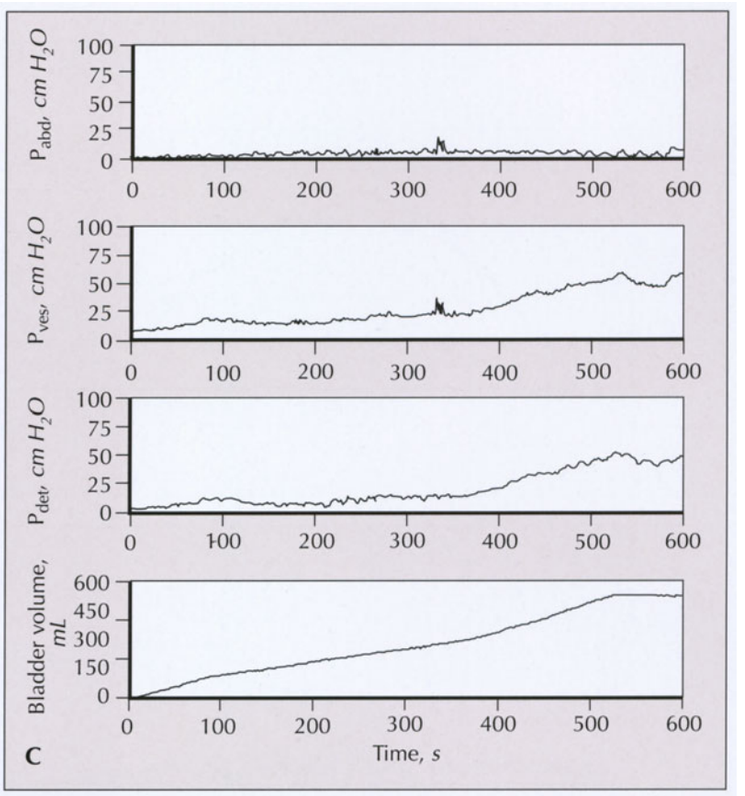

FIGURE 2-5. *(Continued)* **B,** This CMG shows a strong uninhibited detrusor contraction at 190 mL. Stopping the flow of infusant may help distinguish detrusor overactivity from end-fill compliance changes. **C,** In the literature, diminished bladder compliance was arbitrarily defined by the International Continence Society as less 20 mL/cm H_2O [29]. This filling CMG demonstrates an increased slope of detrusor pressure in a patient with bladder outlet obstruction as the bladder was filled beyond 400 mL. This increased slope occurred in the later phase of bladder filling and could be mistaken for the onset of a detrusor contraction. However, the sustained increase in bladder pressure after cessation of bladder filling indicates decreased compliance. In this patient, bladder compliance (10.9 mL/cm H_2O) was considered abnormal, because bladder pressure did not return to baseline after filling stopped.

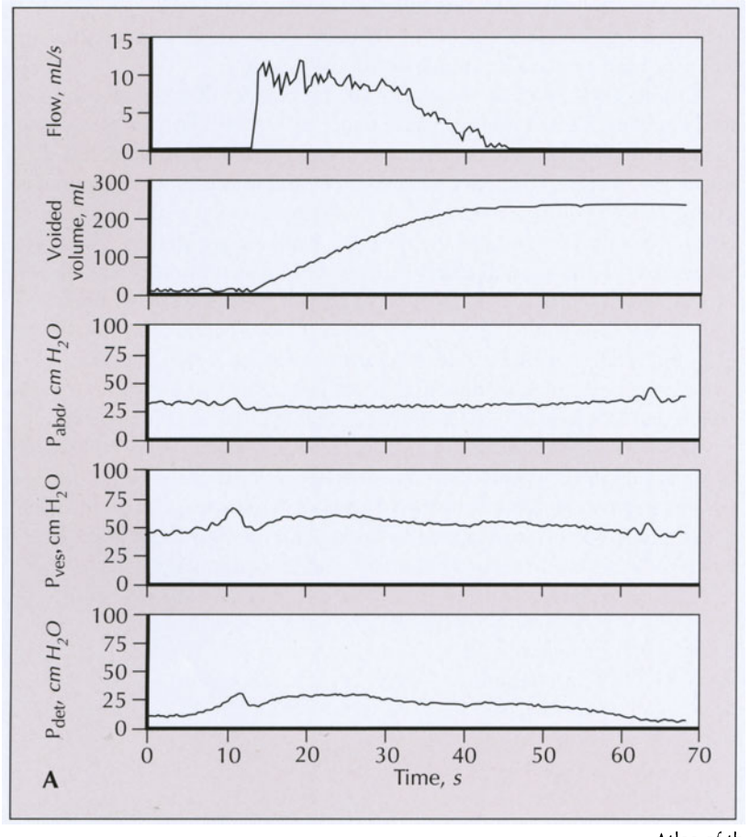

FIGURE 2-6. The pressure-flow study is widely accepted as an important urodynamic step to assess bladder contractility and outlet resistance. Simultaneous intravesical pressure, intrarectal pressure, and urinary flow rate are recorded during voiding in either the sitting or standing positions. This study can be performed under fluoroscopic monitoring to detect bladder changes such as diverticuli and vesicoureteral reflux. The pressure and flow tracings obtained from a nonobstructed (**A**), a mildly obstructed

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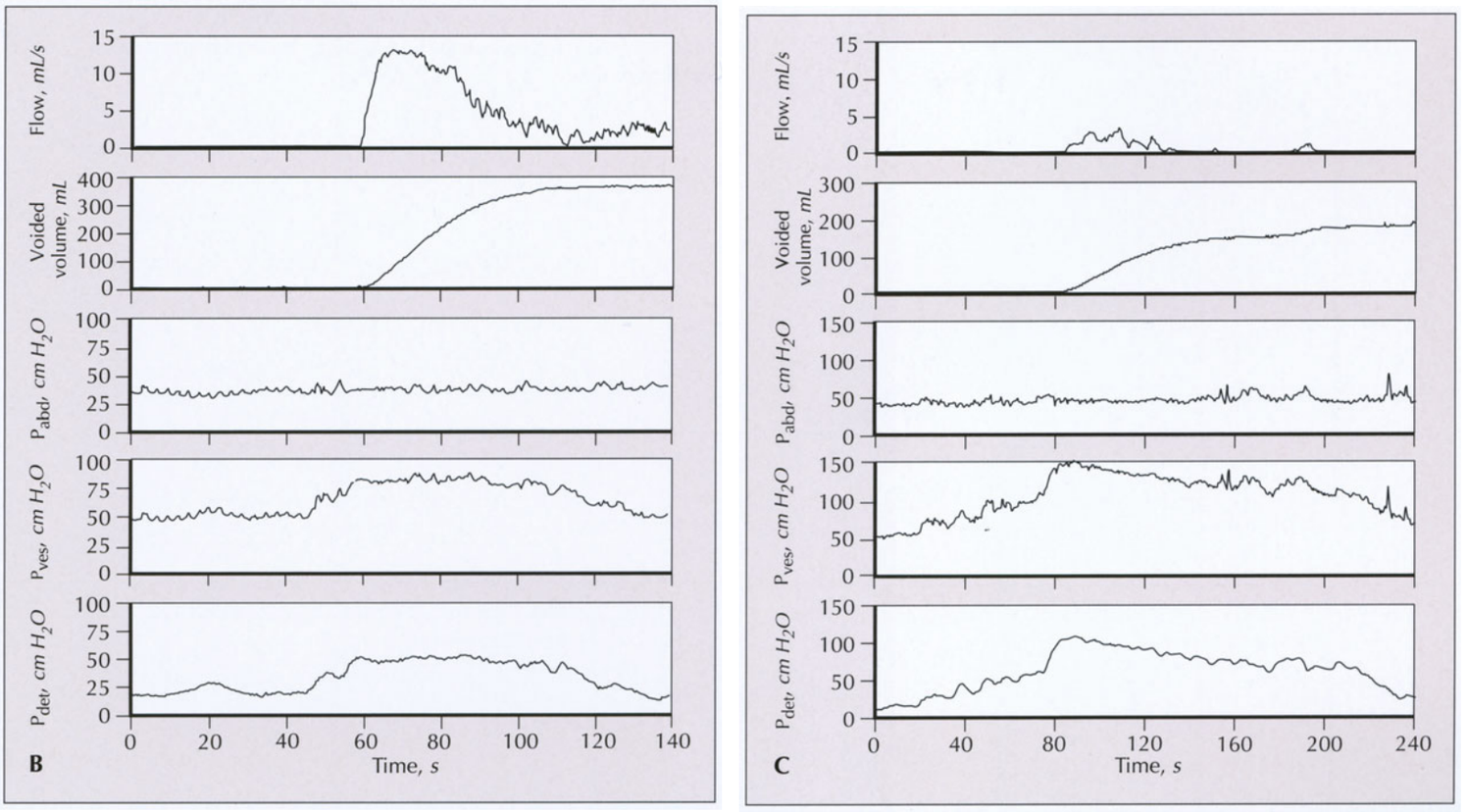

FIGURE 2-6. ***(Continued)*** (**B**), and a severely obstructed (**C**) patient are shown. P_{abd}—abdominal pressure; P_{det}—detrusor pressure; P_{ves}—vesical pressure.

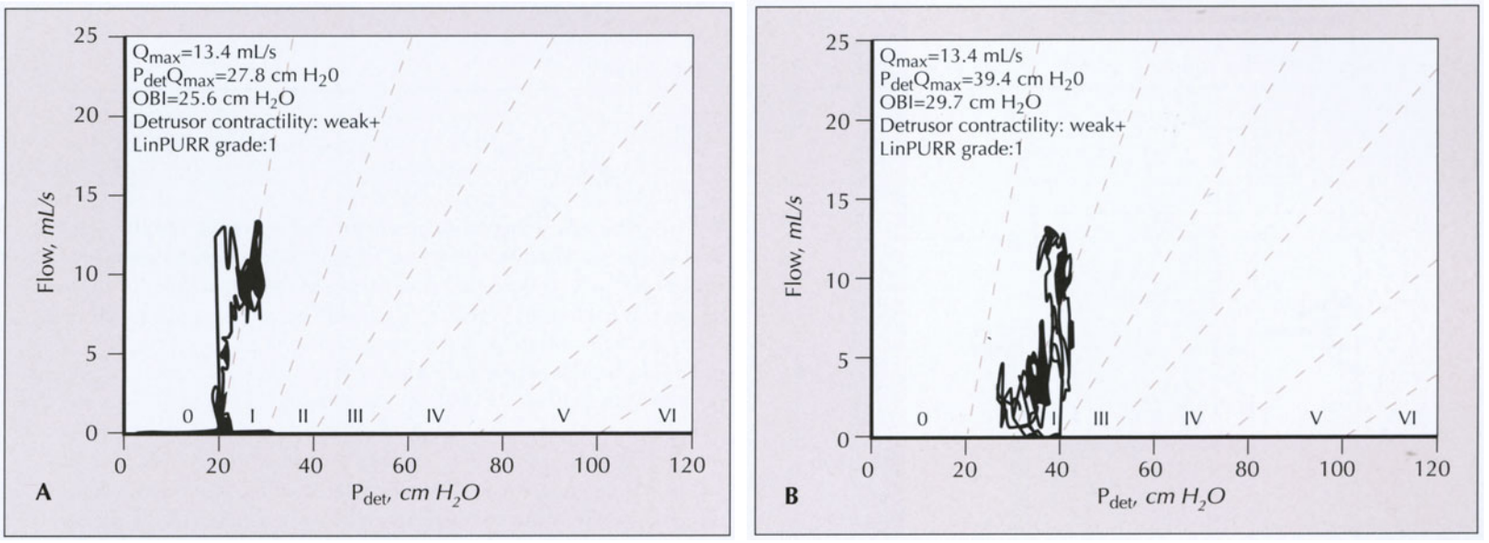

FIGURE 2-7. Pressure-flow (P-Q) studies can be analyzed using a number of sophisticated methods that are based on similar concepts and thus produce fairly comparable results [20]. After eliminating artifacts and correcting the time lag between detrusor pressure and onset of flow, the urinary flow is plotted against the corresponding detrusor pressure during voiding. The nomogram proposed by Schafer for grading bladder outlet obstruction (BOO) is based on the concept of the passive urethral resistance relation (PURR) [30]. PURR represents the passive state of bladder outlet, which is presumed to be free from smooth muscle and striated sphincter influences during voiding. The resistance offered by the bladder outlet under these conditions is assumed to be entirely due to the mechanical properties of the posterior urethra, including the prostate gland. This analysis can be simplified by approximating the PURR with a straight line (LinPURR). LinPURR is graded into six categories (0 through 5), with grade 2 and higher representing BOO. Detrusor contractility is classified in the nomogram as very weak, weak, normal, and strong. The P-Q plots, generated from the same patients studied in Figure 2-6, are superimposed on Schafer's nomogram to determine the severity of BOO and detrusor strength. Data from Figures 2-6*A* and 2-6*B* fall into grade 1 on Schafer's nomogram (**A** and **B**), whereas data

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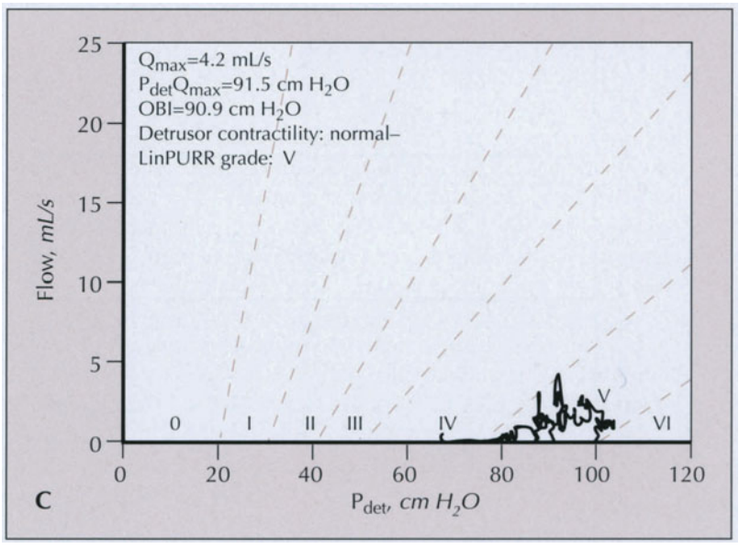
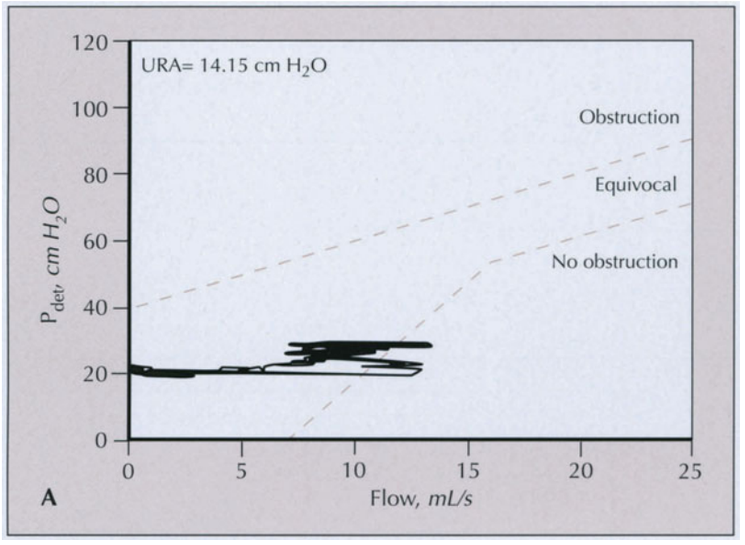
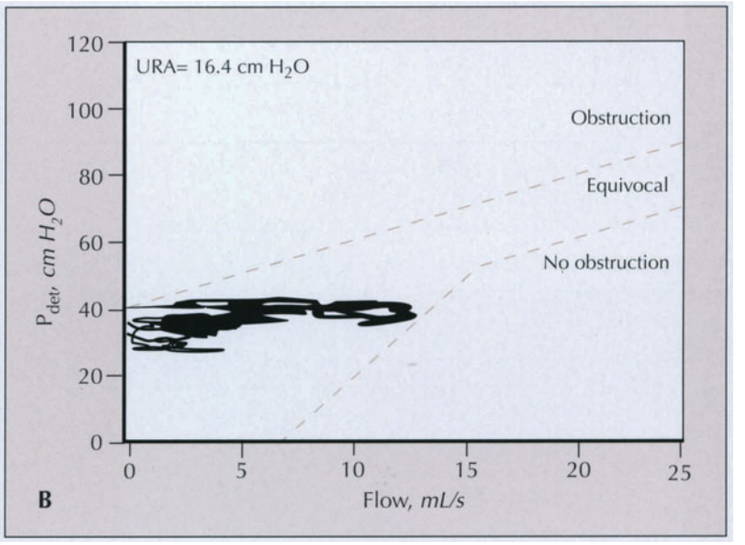


FIGURE 2-7. ***(Continued)*** from Figure 2-6*C* fall into grade 5, indicating severe obstruction (**C**). $P_{det}Q_{max}$—detrusor pressure at maximum flow.





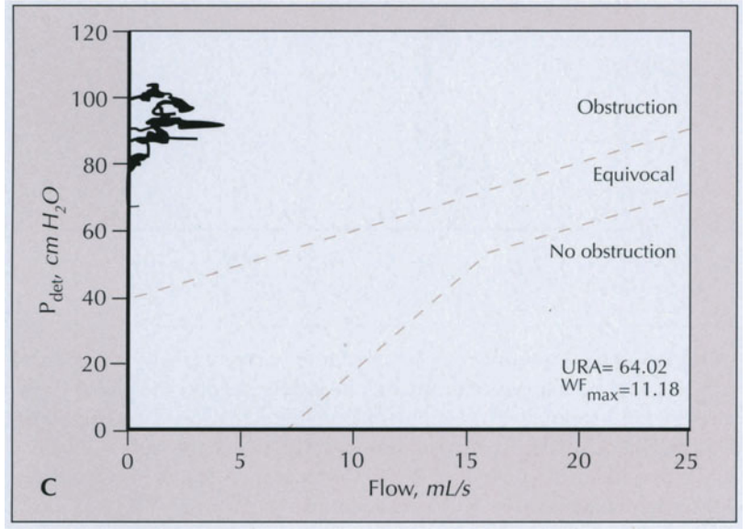


FIGURE 2-8. The Abrams-Griffiths (A-G) nomogram also can be used to characterize the bladder outlet as obstructed, nonobstructed, and equivocal based on the location of the point determined by the detrusor pressure at maximum flow ($P_{det}Q_{max}$) and the maximum flow rate (Q_{max}) [31]. The line on the graph is a continuous plot of P_{det} versus flow. The provisional standard of the International Continence Society for pressure-flow (P-Q) analysis is a modified A-G nomogram in which the slope separating equivocal from unobstructed zones is constant [32]. The A-G number ($P_{det}Q_{max}$ - 2 x Q_{max}) is used to further distinguish equivocal values. Values greater than 40 are correlated with obstruction, whereas values less than 20 are associated with no obstruction. A-G numbers between 20 and 40 are deemed equivocal. The urethral resistance factor (URA), a prostate-specific parameter that approximates the passive urethral resistance relation also can be used to diagnose bladder outlet obstruction on a continuous scale [33]. The P-Q plots generated from the data in Figure 2-6 are superimposed on the A-G nomogram. This analysis results in a diagnosis of no obstruction (**A**), equivocal obstruction (**B**), and obstruction (**C**) for the patients shown in Figure 2-6*A* to *C*, respectively. Detrusor contractility can be assessed by calculating the maximum Watts factor (WF_{max}) [34] or by generating the maximum isovolumetric detrusor pressure (P_{iso}). The Watts factor has been shown to correlate well with P_{iso} [35].

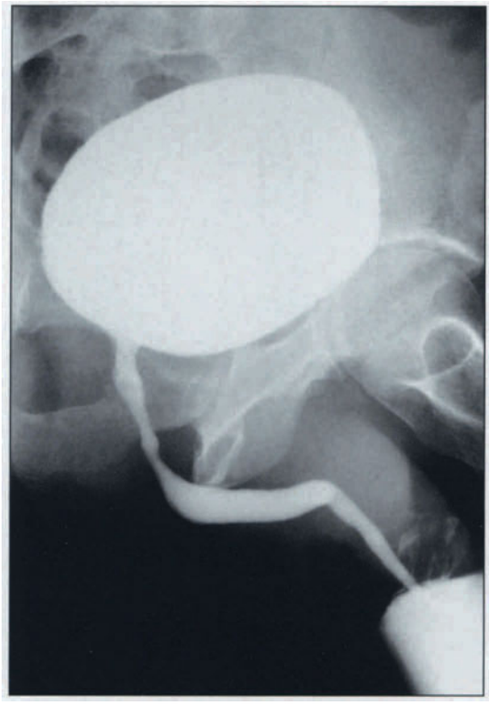


FIGURE 2-9. Normal voiding cystourethrography (VCUG) result. Patients undergoing videourodynamics have the benefit of radiologic imaging of the lower urinary tract to identify significant structural abnormalities that may be associated with voiding dysfunction. When fluoroscopic-assisted urodynamic evaluations are not available, VCUG can be performed as an important adjunct to the functional urodynamic evaluation. By observing the detrusor contour, the degree of bladder neck funneling, the degree of prostatic fossa and bulbous urethral filling, and any degrees of reflux can be determined. This normal VCUG of a 35-year-old asymptomatic volunteer with a normal urodynamic study is characterized by a smooth bladder contour, opened bladder neck and prostatic urethra, and well-distended bulbous urethra. The smooth filling defect in the middle of the prostatic urethra corresponds to the verumontanum.

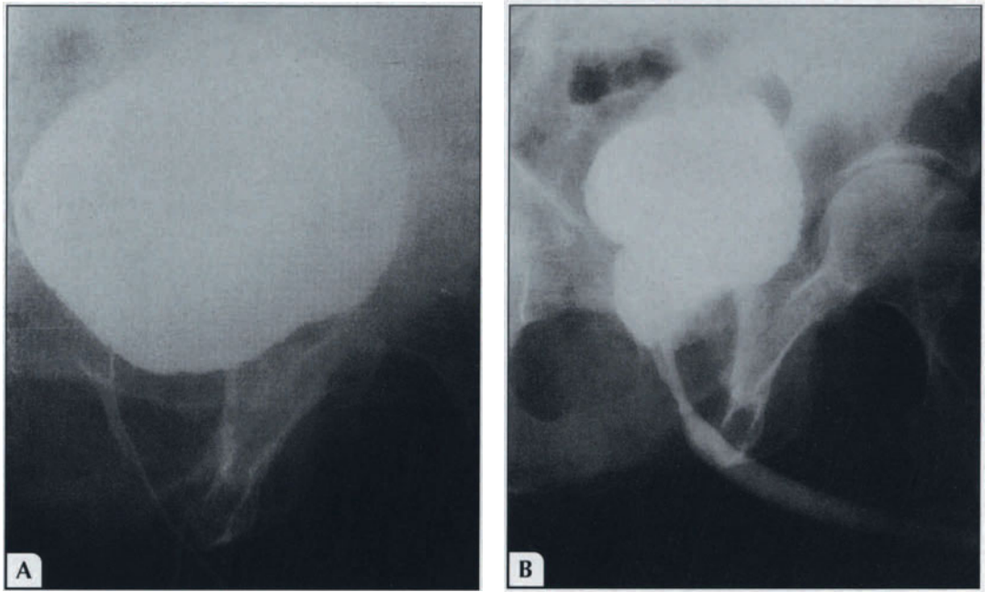


FIGURE 2-10. Abnormal voiding cystourethrography (VCUG) results. **A,** VCUG of an elderly man with lower urinary tract symptoms and radiographic evidence of bladder outlet obstruction. The bladder neck and prostatic urethra appear narrow. **B,** VCUG of an elderly man after transurethral resection of the prostate. The prostatic fossa is wide and the bladder neck is open. There is no evidence of bladder neck contracture or filling defect, suggesting incomplete resection or prostatic regrowth.

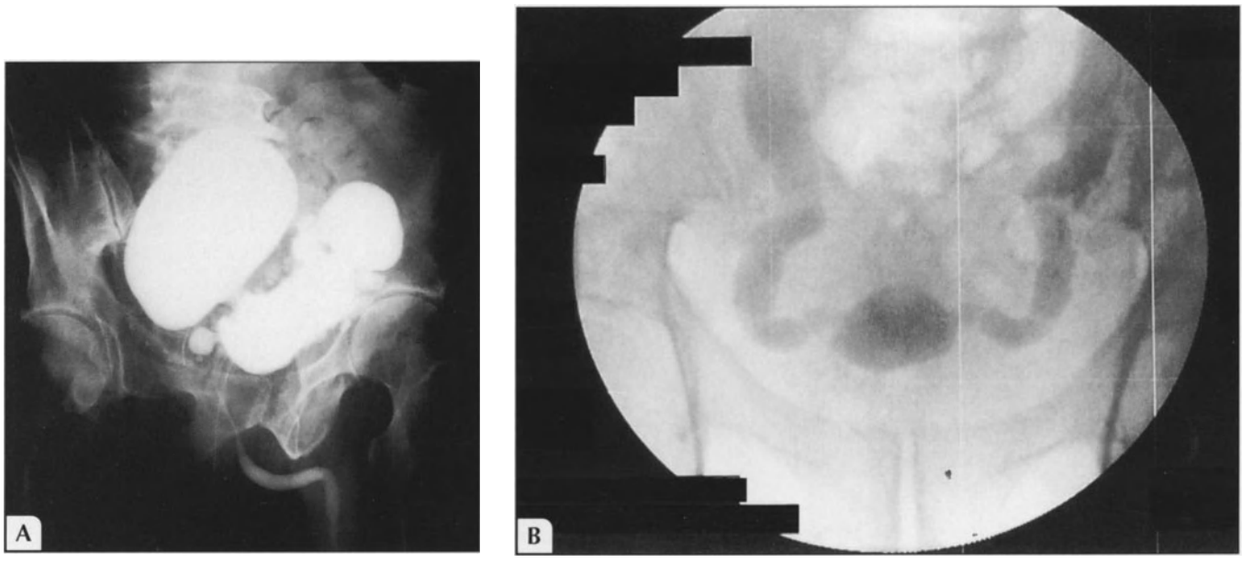


FIGURE 2-11. Large bladder diverticula and high-grade vesicoureteral reflux. These conditions can be the result of chronically elevated vesical pressures. It is important to recognize that both diverticula can confound the urodynamic evaluation by falsely lowering the true bladder capacity and voiding pressure. By providing a venting mechanism to elevated intravesical pressures, they narrow the margin between bladder outlet obstruction (BOO) and detrusor hypocontractility. **A,** Voiding cystourethrogram (VCUG) of an elderly man with lower urinary tract symptoms shows a large bladder diverticulum with a capacity greater than 50% of the total bladder capacity and multiple small diverticula. Bladder diverticula may be congenital but more commonly result from BOO. Diverticula can be the source of recurrent urinary tract infections (persistent contrast in the diverticulum on the postvoid film) or incomplete bladder emptying. **B,** The VCUG of an 80-year-old man with severe lower urinary tract symptoms and a poorly compliant bladder showed high-grade bilateral ureteral reflux with most of the radiocontrast solution entering the renal pelvis and widely dilated ureters. Despite the marked redundancy in the upper urinary tract, the bladder pressures were elevated during filling. His renal function was impaired as demonstrated by elevated serum creatinine and blood urea nitrogen.

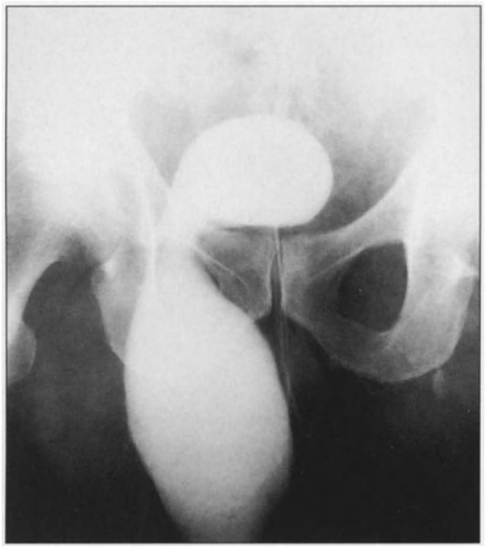


FIGURE 2-12. In some cases, the structural abnormalities identified on voiding cystourethrogram (VCUG) can change the management strategy. This VCUG of a 65-year-old man with an American Urological Association Symptom Index score of 25 shows scrotal herniation of the urinary bladder. Urodynamic evidence of mild outlet obstruction with detrusor instability was noted. Cystoscopy and pressure-flow studies without radiologic assistance would have missed this important structural abnormality. In fact, this patient had been treated for several months with an α-adrenergic blocker (terazosin) without relief of symptoms. Following reduction of a wide-mouthed bladder diverticulum, the direct inguinal hernia was repaired.

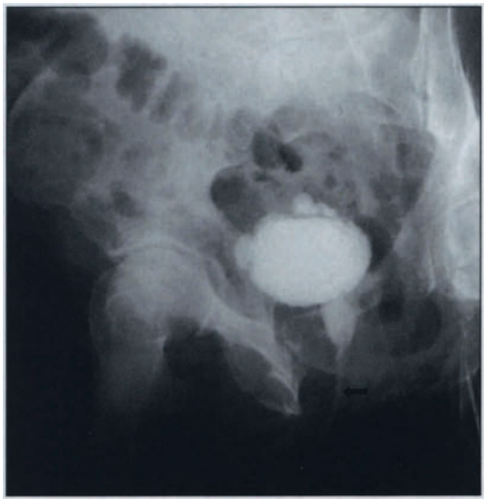


FIGURE 2-13. In patients with bladder outlet obstruction, the site of obstruction cannot be determined by pressure-flow studies, although the prostate is the most likely location in elderly patients with nonneuropathic, nontraumatic lower urinary tract dysfunction. However, this voiding cystourethrogram in an elderly man with lower urinary tract symptoms reveals a narrow membranous urethra with proximal dilation of the prostatic urethra (*arrow*), suggesting obstruction in the region of the membranous urethra but not in the prostatic urethra. Note the small diverticula in the bladder dome.

CYSTOURETHROSCOPY

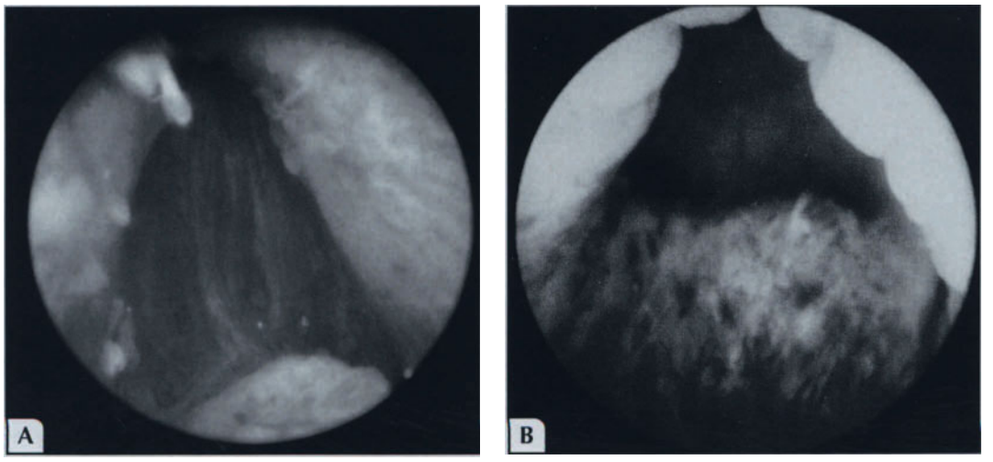


FIGURE 2-14. Because cystoscopy is done in a retrograde fashion, endoscopic findings regarding the prostatic urethra cannot reliably determine bladder outlet obstruction [36]. **A,** Cystoscopy of the bladder neck and midprostatic urethra shows minimal prostatic lobes and a closed bladder neck. No obstruction was found urodynamically. **B,** Up to 25% of patients have median lobe enlargement, which may be responsible for obstruction and lower urinary tract symptoms.

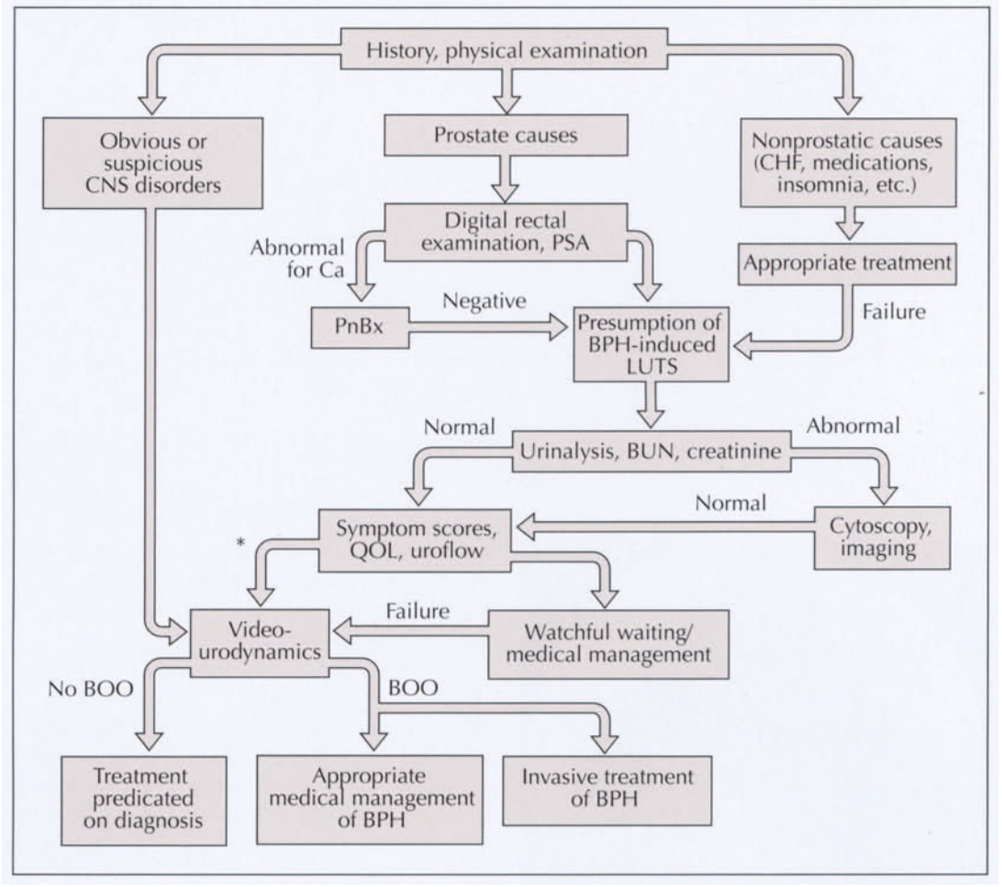


FIGURE 2-15. Algorithm for evaluating adult and elderly men with lower urinary tract symptoms (LUTS). Prostatic causes are separated from other factors that can produce symptoms. After deciding whether benign prostatic hyperplasia (BPH) is presumed responsible for LUTS, the symptom scores decide the remaining part of the work-up of patients with LUTS. The decision to perform cystoscopy, intravenous pyelogram, ultrasonic imaging, or other ancillary tests is prompted by abnormal urinalysis, blood urea nitrogen (BUN), and creatinine, but not by symptom scores alone. The *asterisk* denotes that urodynamic studies are indicated in patients with obvious or suspicious central nervous system (CNS) disorders, in patients who may be candidates for invasive procedures, in younger patients in whom a more accurate diagnosis is required before pharmacologic or surgical intervention, and in frail, elderly patients who are prone to a higher morbidity. BOO—bladder outlet obstruction; CHF—congestive heart failure; PnBX—prostatic needle biopsy; PSA—prostate-specific antigen; QOL—quality of life.

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Medical Management of Benign Prostatic Hyperplasia

3

Timothy D. Moon

With histologic evidence of benign prostatic hyperplasia (BPH) in nearly 50% of men aged 50 years, and prevalence rates increasing with age, BPH is the most common benign neoplasm of elderly men [1]. Bladder outlet obstruction resulting from the hyperplastic prostate is believed to be secondary to two mechanisms: 1) the static component or bulk obstruction caused by the enlarged prostate encroaching on the prostatic urethra, and 2) the dynamic component mediated by smooth muscle tone within the prostatic stroma. Traditionally, surgery has been the mainstay of treatment for symptomatic BPH. However, clinical practice guidelines developed by the Agency for Health Care Policy and Research and endorsed by the American Urological Association were released to serve as a guide for the diagnosis and treatment of patients with BPH [2]. A new edition of these guidelines will be forthcoming in 2003. Treatment is recommended for the majority of patients with moderate to severe symptoms as defined by the American Urological Association symptom score. Medical therapy is among the recommended treatment options. The availability of medical therapy, which is less invasive and therefore more appealing to many patients, has been associated with huge increases in the total number of patients treated compared with the previous era, when surgery was the only option.

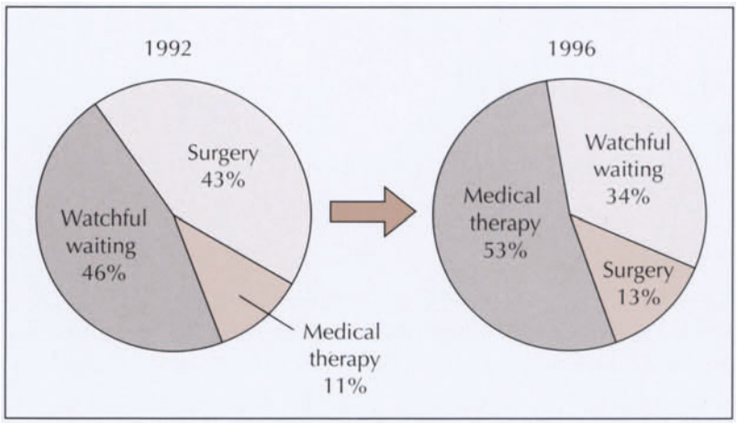


FIGURE 3-1. Impact of medical therapy on treatment trends, 1992 versus 1996. Despite an overall aging of the population and a progressively increasing number of men enrolled in the Medicare program, a recent review of the US Medicare database reveals a continual decline in the annual number of prostatectomies performed for benign prostatic hyperplasia (BPH) [3]. In 1994, 147,300 prostatectomies were performed; but in 2000, only 88,132 were performed. This decline coincides with a progressive annual increase in the number of men choosing medical therapy for BPH [4]. By 2000, there were 4.5 million urologist visits for BPH, and 2.1 million prescriptions for α-blockers were written [5].

Candidates for Medical Therapy

Moderate to severe symptoms
Lack of absolute indications for surgery
- Recurrent urinary retention
- Recurrent or persistent gross hematuria
- Recurrent urinary tract infection
- Bladder stones
- Renal insufficiency

FIGURE 3-2. Candidates for medical therapy. Because the primary indication for intervention in the overwhelming majority of patients with benign prostatic hyperplasia is to improve quality of life by relieving symptoms, the ideal candidate for medical therapy should have symptoms bothersome enough to have a negative impact on his quality of life. This patient should also be motivated to be compliant with a potentially lifelong commitment to taking medication, provided that the medication is effective and the side effects are minimal. Individuals presenting with any of the absolute indications for surgery listed in the Agency for Health Care Policy and Research guidelines should be treated with prostatectomy [2].

Natural History of Benign Prostatic Hyperplasia

Histologic prevalence
- 30% at age 50 y
- 80% at age 80 y

IPSS scores >7
- 12%–26% at age 40–49 y
- 46% at age 70+ y

Likelihood of treatment
- 3/1000 person-years at age 40–49 y
- 30/1000 person-years at age 70+ y

Progression of disease over 5 y
- 37%–42%

Risk of urinary retention over 5 y
- 3%–7%

FIGURE 3-3. Natural history of benign prostatic hyperplasia (BPH). Autopsy studies from many countries show the progressive development of BPH with age [6]. The clinical prevalence is much lower [7,8]. The likelihood of treatment for BPH is related to age and symptomatology (10- and fourfold increase, respectively) [9]. Studies of BPH that include a placebo arm have shown that the majority of men do not have progressive symptoms and 40% may have improvement over a 3-year period [10–12]. IPSS—International Prostate Symptom Score.

Placebo Effect in Benign Prostatic Hyperplasia Studies

↓ Symptom scores
↑ Q_{max}
↑ Prostate volume

FIGURE 3-4. Placebo effect in benign prostatic hyperplasia (BPH) studies. Prospective, randomized, double-blind, placebo-controlled studies are the ideal method to evaluate the clinical efficacy of various treatments for BPH. Analysis of several trials of BPH medical therapy reveals that placebo treatment results in modest but statistically significant improvements in symptom scores and peak flow rates [13,14]. The maximum placebo effect is likely to be noted within the first 6 months of treatment, but beneficial effects of placebo have been noted up to 2 years after starting therapy. Placebo response tends to be greater in patients who are less symptomatic and in those with smaller prostate glands (< 40 g) [13]. Prostate volume continues to increase with time despite placebo therapy [13]. This placebo effect must be kept in mind when judging the efficacy of treatment medication. Q_{max}—maximum urine flow.

Evaluation of Benign Prostatic Hyperplasia Symptoms: the IPPS Score

Questions	*Score*
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0–5*
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0–5
3. Over the past month, how often you have found you stopped and started again several times when you urinated?	0–5
4. Over the past month, how often you have found it difficult to postpone urination?	0–5
5. Over the past month, how often you had a weak urinary stream?	0–5
6. Over the past month, how often have you had to push or strain to begin urination?	0–5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	Once = 1; 5 or more = 5

**0 = Not at all; 1 = less than one time in five; 2 = less than half the time; 3 = about half the time; 4 = more than half the time; 5 = almost always.*

FIGURE 3-5. Evaluation of benign prostatic hyperplasia symptoms: the International Prostate Symptom Score (IPSS). This self-administered questionnaire developed by the American Urological Association assesses urinary symptomatology, both irritative (questions 2,4,7) and obstructive (questions 1,3,5,6). Severity is scored on a scale of 0 to 5 with total scores of 0 to 35 possible. A score of 0 to 7 is considered mild, 8 to19 moderate, and 20 to 35 severe [15].

ALTERING THE STATIC COMPONENT OF BENIGN PROSTATIC HYPERPLASIA THROUGH ENDOCRINE THERAPY

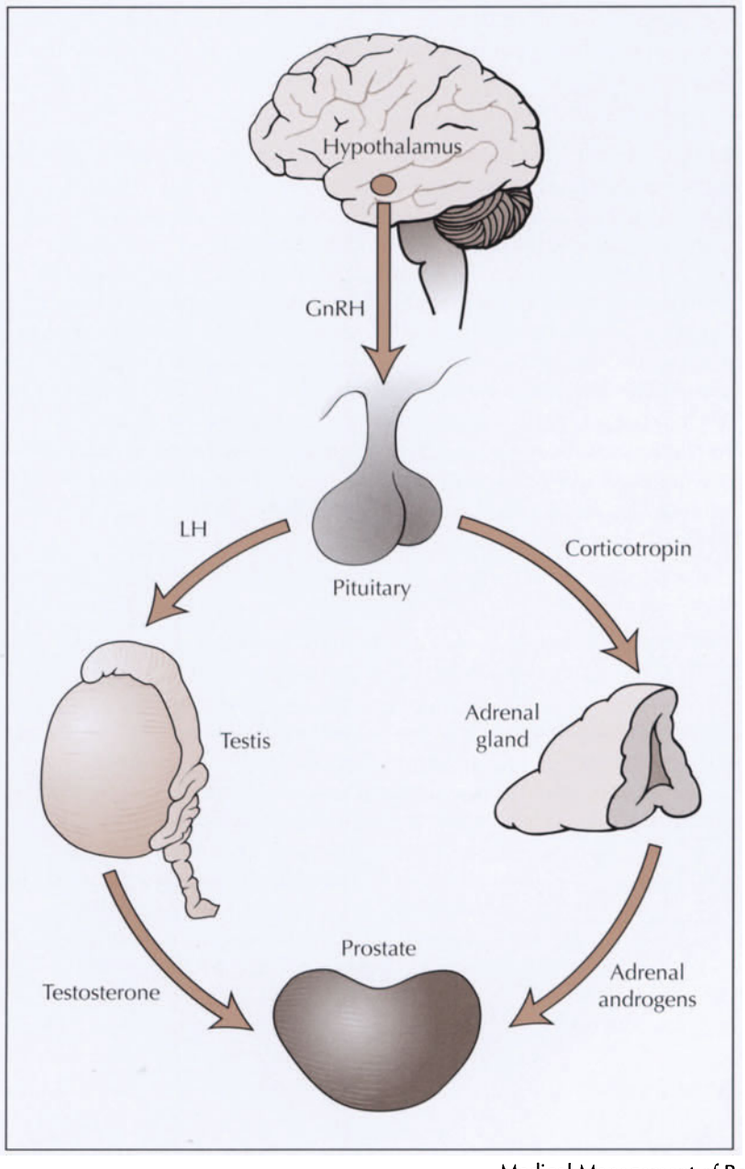


FIGURE 3-6. The hypothalamic-gonadal axis. Adequate levels of circulating testosterone are necessary for the prostate to develop and grow. Gonadotropin-releasing hormone (GnRH) is released in a pulsatile fashion by the hypothalamus into the portal circulation, stimulating the anterior pituitary to secrete luteinizing hormone (LH). LH enters the systemic circulation and then stimulates the Leydig cells of the testes to release testosterone. Of circulating androgens, 95% are composed of testosterone released by the testes, and the other 5% are composed of adrenal androgens, such as dehydroepiandrosterone sulfate. Approximately 98% of circulating androgens are bound to plasma proteins, primarily albumin and sex hormone–binding globulin [16]. Only free testosterone is biologically active and available to enter prostatic cells by a process of simple diffusion.

Clinical Studies of GnRH Agonists and α-Nonsteroidal Antiandrogens in the Treatment of Benign Prostatic Hyperplasia

Study	Agent	Patients, n	↓ Prostate Volume, %	Q_{max}	Symptom Score
Gabrilove *et al.* [17]	GnRH agonist	15	46	↑	↓
Eri and Tveter [18]	GnRH agonist	50	35	↑	↓
Stone *et al.* [19]	Antiandrogen	84	41	↑	↓
Eri and Tveter [20]	Antiandrogen	30	26	↑	↓

FIGURE 3-7. Clinical studies of gonadotropin-releasing hormone (GnRH) agonists and nonsteroidal antiandrogens for the treatment of benign prostatic hyperplasia. As the data demonstrate, these drugs are quite effective in reducing prostate size and improving symptoms. However, their cost and side effects (decreased libido, painful gynecomastia, hot flashes) have excluded these drugs from clinical use. Q_{max}—maximum urine flow.

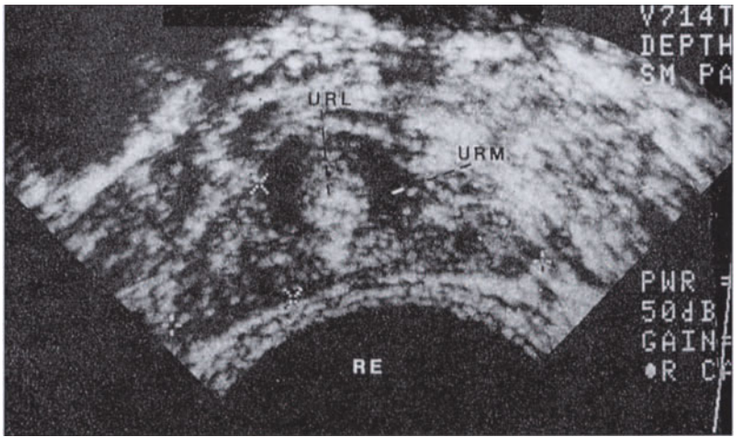


FIGURE 3-8. Clinical support of the dihydrotestosterone (DHT) hypothesis. Transrectal ultrasound of rudimentary prostate (*indicated by cursors*) in male pseudohermaphrodite with 5α-reductase deficiency. Benign prostatic hyperplasia (BPH) does not occur or rarely occurs in men castrated prior to puberty [21]. Numerous clinical studies have documented the regression of BPH and improved voiding symptomatology in men with prostatism following bilateral orchiectomy [22–24]. Male human pseudohermaphrodites resulting from a congenital deficiency of the enzyme 5α-reductase have vestigial prostates, consisting only of a central zone, despite normal serum testosterone levels and no defect in the androgen receptor [25–27]. Administration of DHT results in prostatic growth, indicating that DHT is the primary mediator of prostate growth and that testosterone cannot act alone to support growth and development of the prostate [28]. RE—rectal lumen; URL—urethral lumen; URM—urethromuscular wall. (*Courtesy of* the *Journal of Clinical Endocrinology*.)

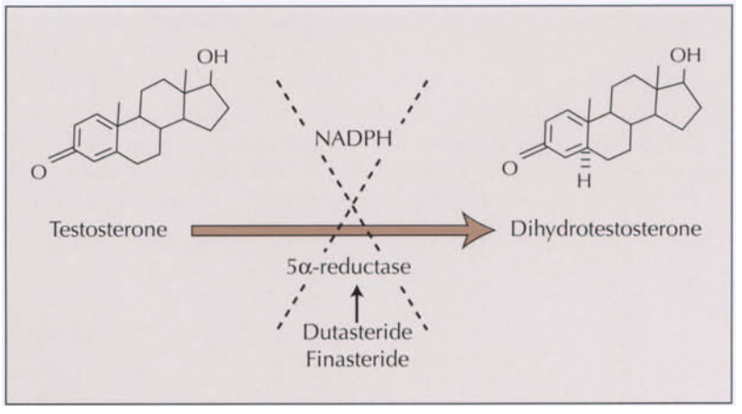


FIGURE 3-9. The mechanism of action of 5α-reductase inhibitors. This mechanism is based on blocking the conversion of testosterone to dihydrotestosterone (DHT) by inhibiting the action of 5α-reductase within cells of the prostate. Two isotypes of 5α-reductase exist, but only 5α-reductase type 2 is detectable within the prostate [29]. Finasteride is a pure 5α-reductase type 2 inhibitor that does not bind the androgen receptor or inhibit the formation or action of other steroid hormones [30]. Administration of finasteride results in an 80% to 90% decrease in the concentration of DHT within both the prostate and the general circulation [31,32]. Accompanying this response is a 560% increase in the local concentration of testosterone within the prostate, without a significant change in the serum concentration of testosterone [33–35]. Dutasteride is a new type I and II 5α-reductase inhibitor that reduces DHT levels by 95% [36]. NADPH—NADPH-ferrihemoprotein reductase.

Randomized, Placebo-Controlled, Double-Blind, Phase III Clinical Trial of Finasteride

Agent	Year	Dose, mg	Follow-up, y	↑ Q_{max}, mL/s (% Change)	↓ Symptom Score (% Change)	↓ Prostate Volume, cm^3 (% Change)
Finasteride [37]	1992	5	1	1.6 (17*)	2.7 (26*)	11.1 (19*)
Placebo	1992	0	1	0.2 (2)	1.0 (1.0*)	1.2 (2)

**Statistically significant with placebo-based values.*

FIGURE 3-10. Results of 1-year clinical trial with finasteride. Entry criteria for initial multicenter, randomized, double-blind, placebo-controlled studies with finasteride included men with lower urinary tract symptoms, a maximum urinary flow rate of less 15 mL/s, and an enlarged prostate on digital rectal examinations. The data revealed a mean decrease in circulating dihydrotestosterone levels of 80% that was sustained without escape during 12 months of treatment and without significant change in circulating serum testosterone levels [37]. Side effects of decreased libido, impotence, and ejaculatory disorder were noted in 3% to 5% of patients. All of these changes were statistically significant compared with findings of the placebo group [37–39]. Q_{max}—maximum urine flow.

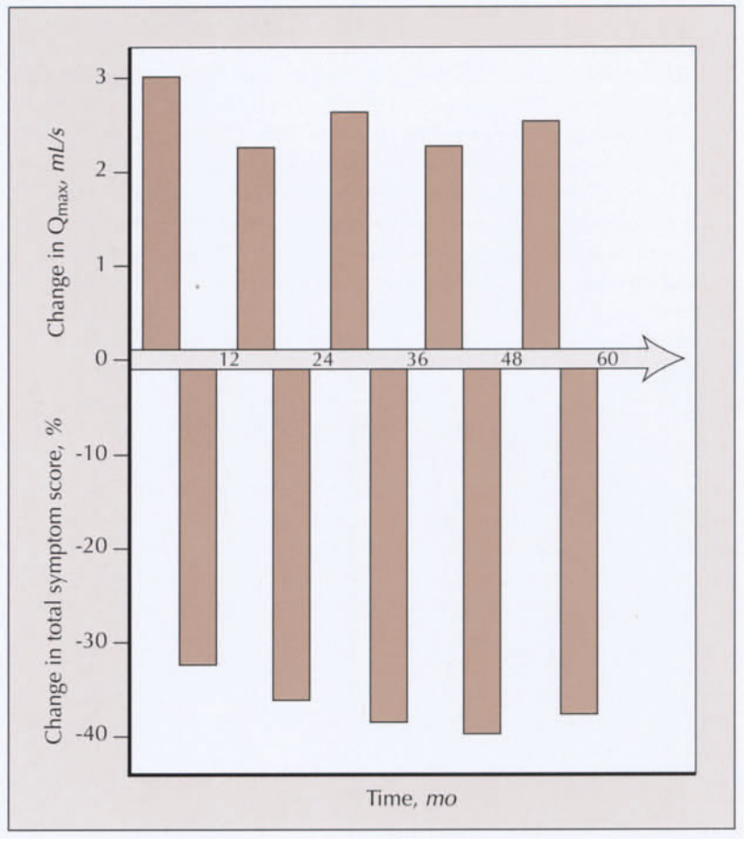
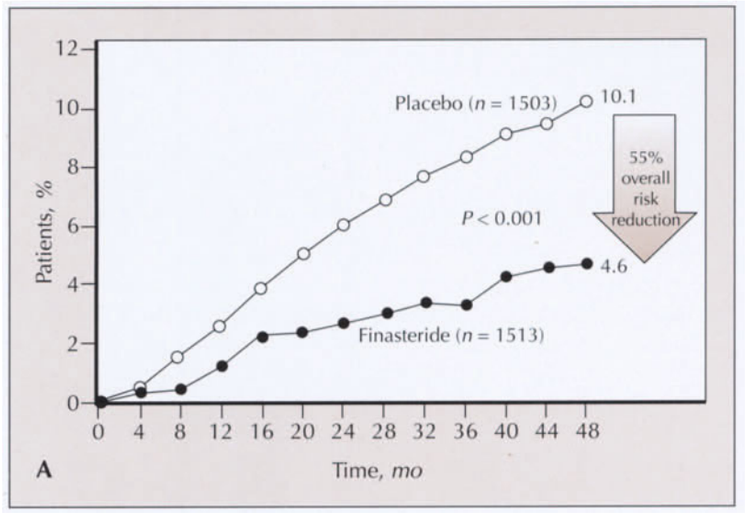


FIGURE 3-11. Long-term clinical results with finasteride. Longer term multicenter placebo-controlled studies, up to 60 months of treatment with finasteride, reveal continued statistically significant improvement in symptom scores, maximum urinary flow rates, and decrease in prostate size when compared with placebo [12]. Men with larger prostates and lower urinary flow rates appear to benefit most from treatment with finasteride [40]. Results of 5-year treatment with finasteride are shown. Q_{max}—maximum urine flow.



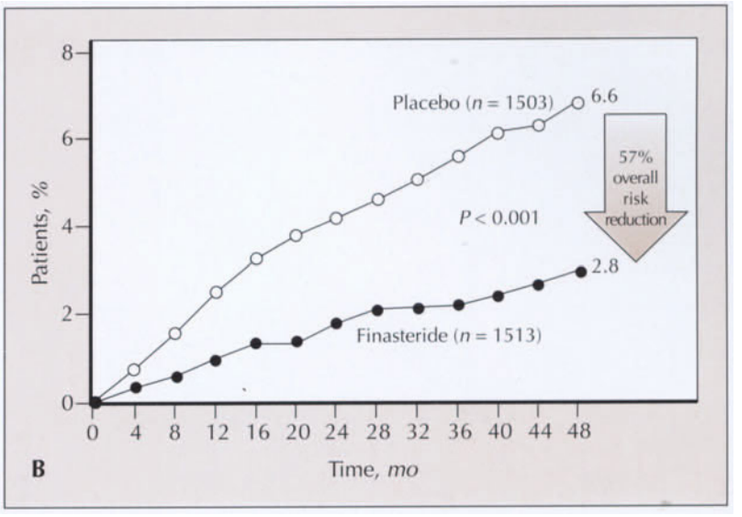


FIGURE 3-12. Effect of finasteride on the risk of acute urinary retention (**A**) and benign prostatic hyperplasia (BPH)-related surgery (**B**). Several large-scale population-based longitudinal epidemiologic studies of aging reveal an increased risk of acute urinary retention and BPH-related surgery (*eg*, transurethral resection of the prostate) over time for men with obstructive urinary symptoms and enlarged prostates [41,42]. Finasteride reduced the risk of acute urinary retention by 57% and the need for BPH-related surgery by 55% compared with placebo during the 4-year study period of a randomized, double-blind, multicenter trial that enrolled over 3000 men. (*Adapted from* McConnell *et al.* [12].)

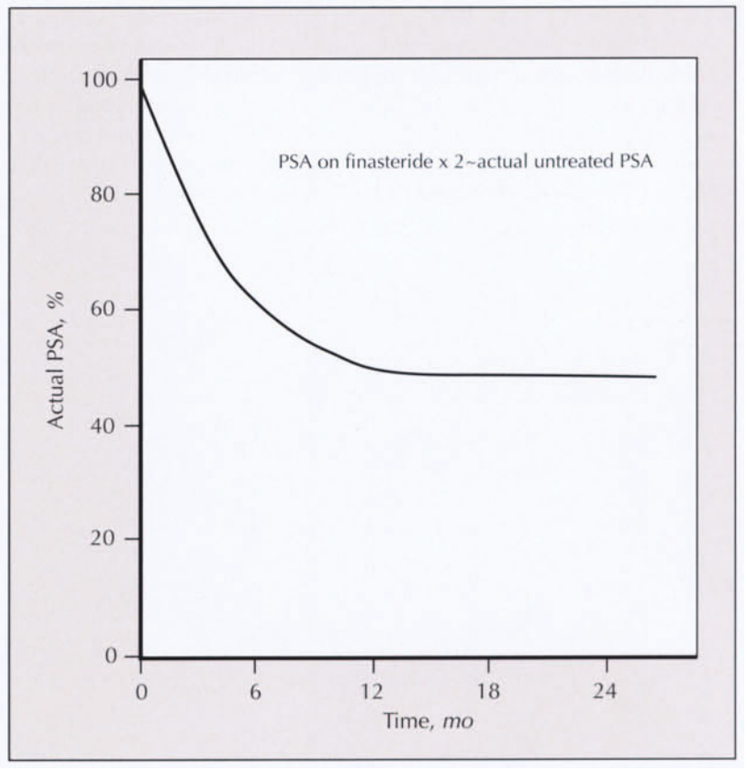


FIGURE 3-13. Effect of treatment with finasteride on prostate-specific antigen (PSA) levels over time. Prostate cancer is the most common nonskin cancer affecting men and the third most common cause of cancer death in American men. Early detection of prostate cancer has been enhanced since the introduction of the PSA screening assay. PSA is an enzyme produced by the prostate and is usually only detectable at low levels in the blood. Most men with prostate cancer have elevated serum levels of PSA. Other variables that can increase PSA levels include prostatitis, prostate infarction, and recent ejaculation. In addition, as prostate volume increases secondary to benign prostatic hyperplasia, PSA values tend to rise. Treatment with finasteride decreases serum PSA levels by approximately 50% [43,44]. Because benign prostatic hyperplasia and prostate cancer can coexist in the same patient, there has been some concern regarding the detection of prostate cancer in patients taking finasteride [45]. Stoner *et al.* [45] showed that despite a 560% decrease in intraprostatic concentrations of testosterone, there appears to be no increased risk of prostate cancer for patients taking finasteride. Doubling the serum PSA for patients taking finasteride and then interpreting the resulting PSA value as in untreated men has been recommended [44]. A recent study by Oesterling *et al.* [46] seems to indicate that doubling PSA levels in finasteride-treated patients allows for appropriate interpretation of PSA and does not mask the detection of prostate cancer. Any sustained increases in PSA levels during finasteride treatment should be carefully evaluated, including consideration of noncompliance with therapy. To date, no clinical benefit has been demonstrated in prostate cancer patients treated with finasteride.

Adverse Effects of Hormonal Therapy

Effect	*GnRH Agonists, %*	*Antiandrogens, %*	*5α-Reductase Inhibitors, %*
Impotence	95–100	10–20	3–4
Loss of libido	95–100	10–20	4–5
Ejaculatory disorder	—	—	4–5
Hot flashes	95–100	—	—
Gynecomastia	0–5	50–100	—
Diarrhea	—	50	—

FIGURE 3-14. Adverse effects of hormonal therapy. The most deleterious effects of agents that alter the hypothalamic-gonadal axis at different levels along the pathway are related to varying degrees of sexual dysfunction. Interventions that markedly lower serum testosterone levels are associated with greater degrees of sexual dysfunction (*eg*, loss of libido) than are agents that block the effect of testosterone on target organs [47]. GnRH—gonadotropin-releasing hormone.

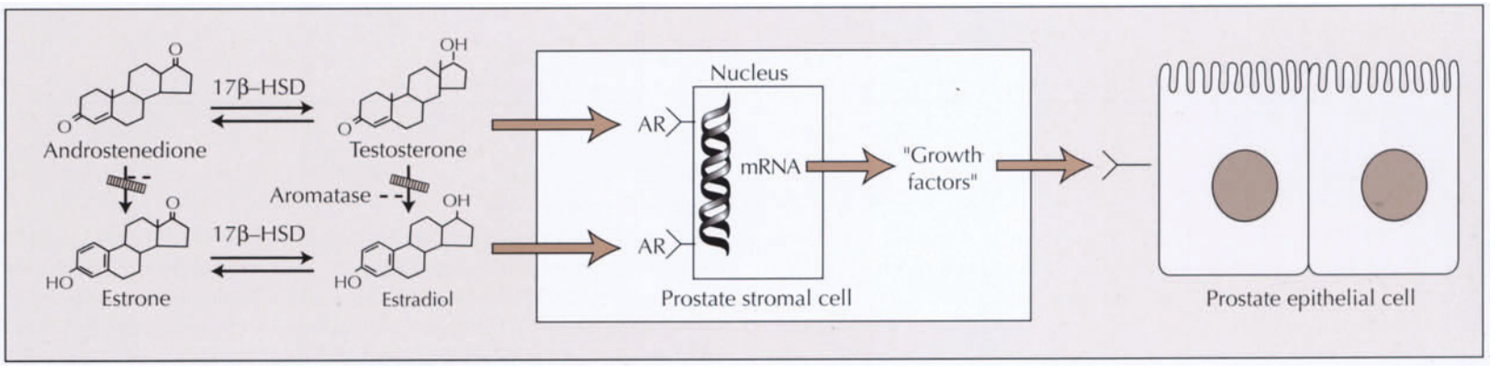


FIGURE 3-15. Effects of estrogens on the pathophysiology of benign prostatic hyperplasia (BPH). As men age, there is a direct correlation between prostate volume and increased serum levels of free testosterone, estradiol, and estriol [48]. In a canine model of BPH, experiments have shown estrogens to act synergistically with androgens in the formation of BPH by inducing the androgen receptor, promoting increased prostatic concentrations of dihydrotestosterone, and reducing the rate of prostate cell death [49–51]. BPH can be induced in castrated dogs via supplementation with aromatizable androgens, and this effect can be blocked by concomitant administration of aromatase inhibitors that prevent conversion of testosterone to estrogen [52]. Clinical studies using aromatase inhibitors, such as atamestane or testolactone, as monotherapy for the treatment of BPH have failed to yield encouraging results [53]. Failure of aromatase inhibitors to improve BPH symptomatology may be related to a simultaneous rise in testosterone concentration that leads to glandular epithelial hyperplasia of the prostate [53]. AR—androgen receptor; 17β-HSD—17β-hydroxysteroid dehydrogenase.

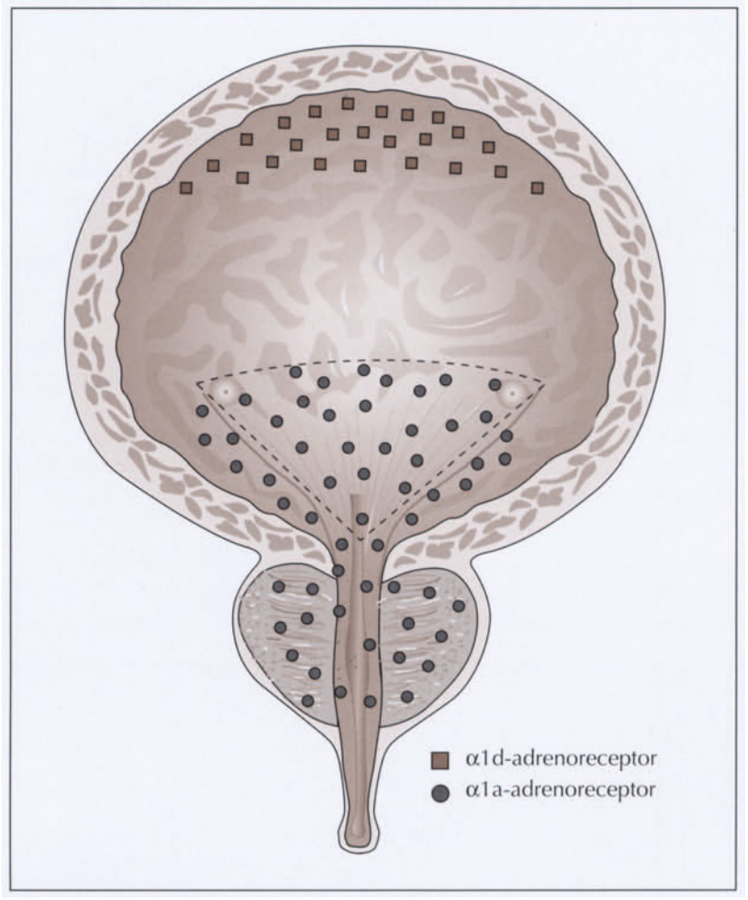


FIGURE 3-16. Distribution of α-adrenoreceptor subtypes in the lower urinary tract [54]. α1a-Receptors predominate in the prostatic epithelial tissue, bladder trigone, and the urethra. α1d-Receptors predominate in the bladder. α1a-Receptors also predominate in the prostatic vascular smooth muscle. However, with aging α1b-receptors are expressed and ultimately predominate. This transition occurs around age 50 years. Thus blockade of α1a-receptors is believed to improve obstructive symptoms by decreasing the prostatic obstruction, while blockade of α1d-receptors is believed to relieve irritative symptoms by reducing bladder tone.

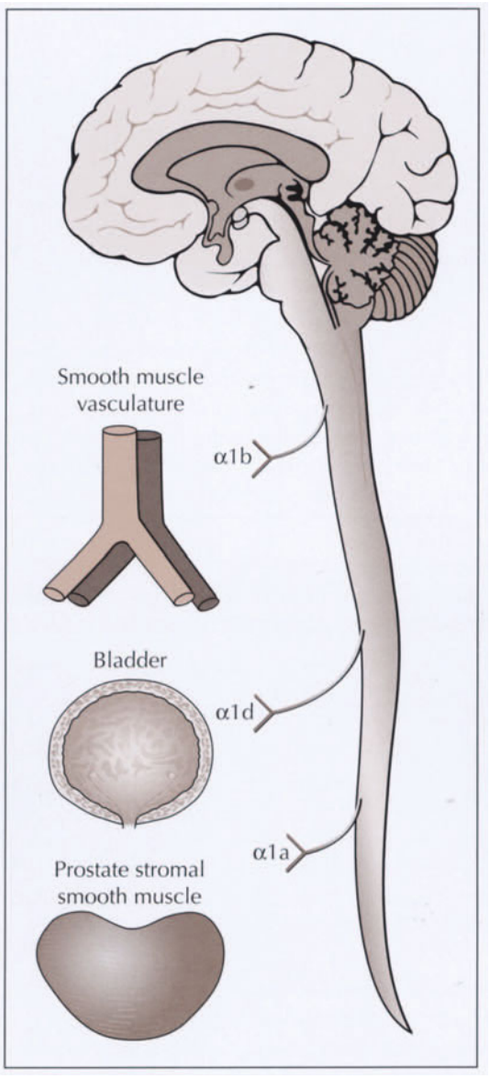


FIGURE 3-17. Distribution of α1-adrenoreceptor subtypes. α-Receptors are distributed ubiquitously throughout the human body [55]. There are two different subtypes of the α-receptor [56,57]. α2-Receptors are located presynaptically and cause downregulation of norepinephrine release via negative feedback [55,56]. α1-Adrenoreceptors are further categorized into α1a, α1b, and α1d subtypes [54–56]. α1b-Receptors are located in the smooth muscle of arteries and veins. Blockade of these α1b-receptors in the cardiovascular system leads to a decreased total peripheral resistance via veno- and arterial dilatation. Such blockade may cause dizziness and hypotension. α1d-Receptors are located in the bladder body. Blockade of these receptors will reduce irritative voiding symptoms. α-1d receptors are also present in the spinal cord and suggest sympathetic modulation of parasympathetic activity [58]. Within the prostate, α1a-Receptors are the predominant subtype, with a smaller proportion of α1b-receptors located in the prostate microvasculature [54,57]. Contraction of prostate smooth muscle is believed to be mediated via the α1a-receptor [54]. Blockade of these receptors will reduce prostatic tone and improve the dynamic aspects of voiding.

Randomized, Placebo-Controlled, Double-Blind Phase III Clinical Trials of Terazosin

Study	Year	Patients, n	Dose, mg	Follow-up, wk	↑ Q_{max}, mL/s	↓ Symptom Score, %
Fabricius and MacHannaford [59]	1990	30	10	12	2.3*	NR
Lepor *et al.* [60]	1992	285	2–10	12	0.7–1.3*	23–44*
Lepor *et al.* [61]	1992	199	2–20	24	1.5*	33*
Brawer *et al.* [62]	1993	160	1–10	24	1.4*	31*
Debruyne *et al.* [63]	1995	427	5–10	26	3.2*	55*
Roehrborn *et al.* [64]	1996	2084	2–10	52	2.2*	38*

* *Statistically significant compared with placebo-based values.*

FIGURE 3-18. Randomized, placebo-controlled, double-blind phase III clinical trials of terazosin. The efficacy of terazosin, a long-acting selective α1-blocker that allows for once-daily dosing, has been documented in numerous clinical trials [59–64]. The largest of these clinical trials, the Hytrin Community Assessment Trial, is representative of results obtained in patients treated with terazosin [64]. This study enrolled 2084 men at least 55 years of age with moderate to severe symptoms of benign prostatic hyperplasia and peak urinary flow rates less than 15 mL/s. Patients were randomly assigned to treatment with either placebo or terazosin in a titrate to effect dosing. After 1 year of treatment, peak flow increased an average of 2.2 mL/s, and symptom scores decreased a mean of 38% compared with baseline. Both changes were statistically significant compared with the findings from placebo. In addition, quality of life score was significantly improved in the terazosin-treated group versus the placebo-treated group. Treatment failure occurred in 11% of the terazosin group. Withdrawal from the study due to adverse effect of treatment occurred in 20% of the terazosin group. NR—not reported; Q_{max}—maximum urine flow.

Randomized, Placebo-Controlled, Double-Blind Phase III Clinical Trials of Doxazosin

Study	Year	Patients, n	Dose, mg	Follow-up, wk	↑ Q_{max}, mL/s	↓ Symptom Score, %
Gillenwater and Mobley [65]	1993	100	8	6	2.9*	56*
Janknegt and Chapple [66]	1993	456	1–16	4–29	1.2–3.9*	NR
Chapple *et al.* [67]	1994	135	4	12	1.0	NR
Holme *et al.* [68]	1994	100	4	29	1.7*	NR
Fawzy *et al.* [69]	1995	100	2–8	16	2.9*	40*
Gillenwater *et al.* [70]	1995	216	2–12	16	2.3–3.6*	NR
Kirby [71]	1995	232	4	9–12	2–2.4*	NR

* *Statistically significant compared with placebo-based values.*

FIGURE 3-19. Randomized, placebo-controlled, double-blind phase III clinical trials of doxazosin. Doxazosin is also a long-acting selective α1-blocker allowing for once-daily dosing. Short-term clinical trials have shown doxazosin to increase peak flow rates by about 1 to 4 mL/s and decrease symptom scores by 30% to 50% in men with symptomatic benign prostatic hyperplasia (BPH) [65–71]. The clinical response to α-blockers in terms of decreased symptomatology and increased flow rates in men with symptomatic BPH is dose dependent; however, the side effect profile is also dose dependent. Studies attempting to determine variables (*eg*, patient age, prostate size, total symptom score, flow rate) that are predictive of the clinical response to α-blockers have failed to delineate a significant association between baseline factors and treatment effect. NR—not reported; Q_{max}—maximum urine flow.

Randomized, Placebo-Controlled, Double-Blind Phase III Clinical Trials of Tamsulosin

Study	Year	Patients, n	Dose, mg	Follow-up, wk	↑ Q_{max}, mL/s	↓ Symptom Score, %	PVR, %
Abrams *et al.* [73]	1995	296	0.4	12	1.4*	36*	21*
Lepor *et al.* [74]	1995	1488	0.4	13	1.8*	42*	NR
Chapple *et al.* [75]	1996	575	0.4	12	1.6*	35*	23*

**Statistically significant compared with placebo-based values.*

FIGURE 3-20. Randomized, placebo-controlled, double-blind phase III clinical trials of tamsulosin. Pharmacokinetic studies have demonstrated tamsulosin to be a long-acting α-blocker with selectivity for the α1a-adrenoreceptor [72]. Theoretically, a prostate-specific α-blocker would maximize clinical efficacy while minimizing side effects. Short-term clinical studies to date have shown tamsulosin to increase peak flow rates approximately 1.5 mL/s and to decrease symptom scores by about 35% [74–76]. The side effect profile appears similar to that of other long-acting agents such as terazosin or doxazosin. Longer term clinical trials are pending. NR—not reported; PVR—postvoid residual volume; Q_{max}—maximum urine flow.

Randomized, Placebo-Controlled, Double-Blind, Phase III Clinical Trials of Alfuzosin

Study	Year	Patients, n	Dose, mg	Follow-up, wk	↑ Q_{max}, mLs	↓ Symptom Score, %
Jardin *et al.* [77]	1991	518	2.5 TID	26	+1.4	42
Hansen *et al.* [78]	1994	178	2.5 TID	12	+2.0*	29*
Buzelin *et al.* [79]	1997	382	5 mg SR BID	12	+2.4*	33*
Kerrebroeck *et al.* [80]	2000	297	10 mg XL OD	12	+2.3*	40*

*Statistically significant with placebo-based values.

FIGURE 3-21. Randomized, placebo-controlled, double–blind phase III trials of alfuzosin. Alfuzosin is a short-acting selective α1-blocker. It has been approved in Europe for 10 years. The manufacturers, by changing the formulation, have moved from a three times per day drug to a once-daily formulation. It is anticipated that the once-daily formulation will be approved in the United States in the near future. Overall its efficacy is similar to other α-blocking agents. Q_{max}—maximum urine flow; SR BID—sustained-release twice daily; TID—three times daily; XL OD—extra-large once daily.

Long-term Use of Drugs for Benign Prostatic Hyperplasia

Study	Drug	Duration, y	Patients, n	New Adverse Effects	Continued Efficacy in Responders	Overall Dropout Rate, %
Lepor [81]	α-Blocker	4	494	No	Yes	43
Lepor *et al.* [82]	α-Blocker	4	450	No	Yes	51
Narayan *et al.* [83]	α-Blocker	5–6	419–109	No	Yes	24
Djavan and Marberger [84]	5α-Reductase inhibitor	4	1524	No	Yes	34

FIGURE 3-22. Long-term use of medical therapies for benign prostatic hyperplasia. This figure summarizes the efficacy and safety data for medical therapies over longer periods. Patients were recruited de novo into the 5α-reductase study while the α-blocker studies followed patients who had previously been in other trials using the same drug. As noted in the figure, new adverse events did not occur and efficacy continued throughout the study period. However, the end point data from all the studies reflect "responder" data. As patients dropped out of the studies (24%–51%), their (generally) negative data were also dropped, allowing the studies to "demonstrate" continued efficacy for the period of the study.

Adverse Effects of α-Blockers

Effect	Prazosin, %	Phenoxybenzamine, %	Terazosin, %	Doxazosin, %	Tamsulosin, %
Hypotension	10–15	15–20	2–8	1–2	<1
Dizziness	15–17	10–14	7–14	10–15	15
Headache	13–15	4–15	4–10	9–10	19
Sexual dysfunction	NI	5–8	2–7	NI	8
Fatigue	10	10–15	4–8	1–2	8
Syncope	NI	NI	<1	<1	<1
Nasal congestion	NI	8	2	NI	13

FIGURE 3-23. Adverse effects of α-blockers [47,81–84]. Dizziness is the most common side effect and may be unrelated to α-antagonist effects on the blood vessels themselves. The fact that some dizziness is seen with tamsulosin suggests that a central effect may mediate this symptom. Hypotension decreases with longer acting drugs and is least with uroselective agents (tamsulosin). Concurrent use of tamsulosin with other hypotensive agents has been safely administered. Dizziness and hypotension are more common in those over 65 years of age. Ejaculatory dysfunction may occur, but when explained to the patient does not generally cause a problem. Its effect may be mediated through effects on the vas itself.

Combination Therapy for the Treatment of Benign Prostatic Hyperplasia

Agent	Patients, n	Q_{max}, mL/s	Symptom Score, units	Prostate Volume, mL
Placebo	254	1.4	-2.6	0.5
Terazosin	256	2.7	-6.1	0.5
Finasteride	243	1.6	-3.2	-6.1
Terazosin + finasteride	254	3.2	-6.2	-7.0

FIGURE 3-24. Combination therapy for the treatment of benign prostatic hyperplasia (BPH). The Veterans Affairs Cooperative Study [85] attempted to determine whether terazosin, finasteride, or a combination of the two resulted in clinically superior results for the treatment of BPH. In this multicenter, double-blind trial, patients were randomly assigned to treatment with placebo, terazosin, finasteride, or a combination of terazosin and finasteride. After 1 year of treatment, the investigators concluded that terazosin alone produced superior results in terms of improvement in symptom score and peak urinary flow rates. The applicability of this study's conclusion to the general population of men with symptomatic BPH has been challenged because of the relatively small percentage of men with larger prostates included in this study [86]. Q_{max}—maximum urine flow.

Overview of Phytotherapy

- Phytotherapeutics have been used for prostate problems for hundreds of years
- Use of botanicals for BPH averages $80 million per year
- Phytotherapeutic agents hold 50% of the BPH market in Italy compared with 5% each for α-blockers and 5α-reductase inhibitors
- Because as chemicals they are not patentable, they have been poorly studied
- Published data suggest that β-sitosterol is better than current prescription drugs

FIGURE 3-25. Overview of phytotherapy. Botanicals remain the lifeblood of modern pharmacology. The most famous is probably the foxglove plant, but serenoa repens has been used for the prostate for over 300 years [87]. Despite the fact that Americans use more and more alternative medicine [88], and that the use of botanicals in Europe far exceeds that for α-blockers and 5α-reductase inhibitors [89], the plant extracts have been poorly evaluated. This is primarily due to their sale as food supplements and not pharmaceuticals that may be patented.

Phytotherapeutic Agents

Plant	Common Name	Trade Name	Active Agent	Method of Action
Serenoa repens	Saw palmetto	Permixon	Fatty acids, sterols	Antiandrogen β-FGF, EGF
Pygeum africanum	African prune	Tadenan	β-Sitosterol	Cholesterol mechanism
			Fatty alcohols	Inhibits β-FGH
			Fatty acids	EGH
				Anti-inflammatory
Hypoxis rooperi	South African star grass	Harzol	β-Sitosterol	Anti-inflammatory
				Anticholesterol metabolism
Dinus picea	Pine flower spruce	Azurusat (combination)	β-Sitosterol	Anti-inflammatory
				Anticholesterol metabolism
Secale cereale	Rye grass pollen	Cernilton	β-Sterols	Antiandrogen
				Inhibitors of prostaglandins
				Leukotriene synthesis

FIGURE 3-26. Phytotherapeutic agents. The true chemical nature of these plant extracts is generally unclear. The listed "active" agent represents only one of the no doubt many active ingredients. In general the components of plant extracts are phytosterols, phytoestrogens, and terpenoids [90]. Likewise the postulated action is often broader than shown in the figure [90]. Unfortunately many of these studies evaluating the mechanism of action have used supraphysiologic doses of the extracts [90]. EGF—epidermal growth factor; EGH—equine growth hormone; β-FGF—β-fibroblast growth factor.

Placebo-controlled Trials of Phytotherapeutics

Herb	Patients, n	Studies, n	Duration, wk	↓ Symptoms, %	↑ Peak Flow, %
Saw palmetto	2939	18	4–48	28	26
Hypoxis rooperi (β-sitosterol)	519	4	4–26	50	67
Secale cereale	163	2	12–26	69	9

FIGURE 3-27. Results of placebo-controlled trials. Many of the drug trials have been small, of short duration, and not placebo controlled. This is in part explained by the fact that the compounds are not patentable or considered pharmaceuticals. There is, therefore, no need or money to fund large multimillion-dollar drug trials. The data shown in the figure demonstrate activity of many of these agents. β-sitosterol would appear, based on these data and longer term follow-up [91], to be possibly better than the pharmaceuticals currently available. They are also much cheaper.

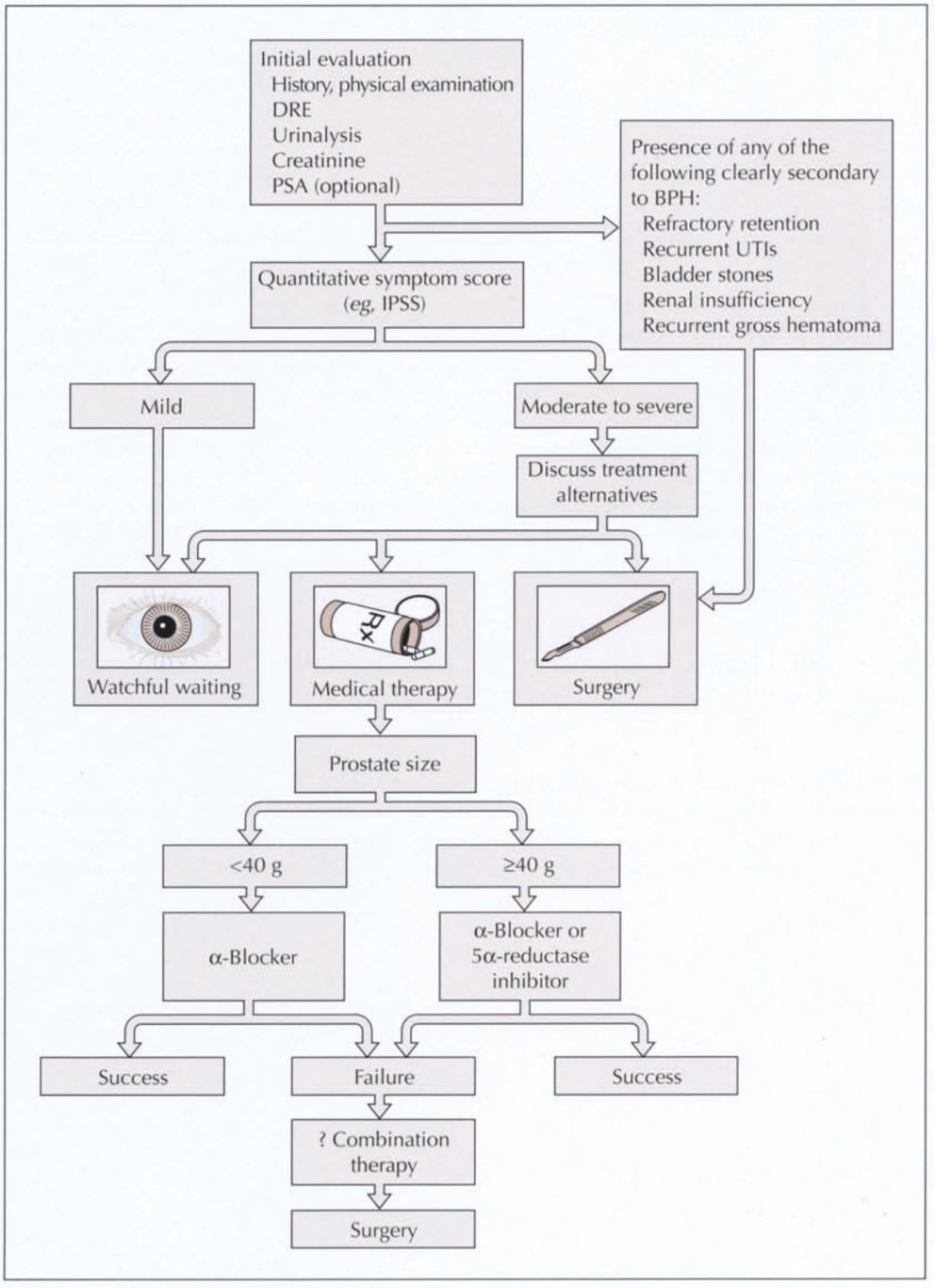


FIGURE 3-28. Treatment algorithm for symptomatic benign prostatic hyperplasia (BPH). In general, highly symptomatic patients or patients suffering from acute urinary retention tend to respond more rapidly to treatment with α-blockers than to other currently available agents. Therefore, when prompt symptomatic relief is of utmost importance, α-blockers are a logical first-line treatment choice in men with moderate to severe symptoms, seeking medical treatment. For men with prostate glands 40 g or larger, finasteride should be given consideration as either monotherapy or combination therapy with an α-blocker. DRE—digital rectal examination; IPSS—International Prostate Symptom Score; PSA—prostate-specific antigen; UTI—urinary tract infection.

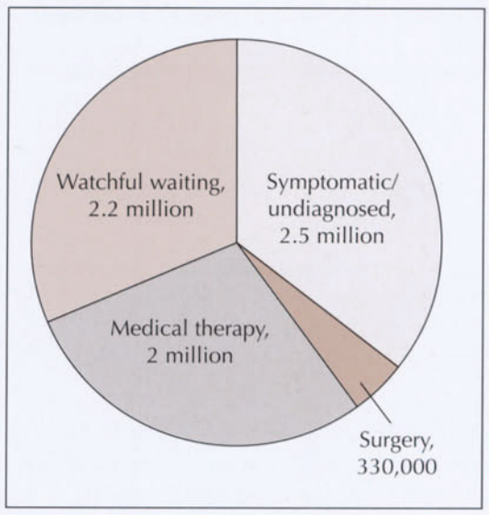


FIGURE 3-29. Prevalence of benign prostatic hyperplasia (BPH) and treatment trends. BPH will remain the predominant disease that urologists treat. As the average life span continues to increase, the number of potential patients with symptomatic BPH will continue to rise. Most recent statistics show that, currently, 6 million men suffer from clinical BPH. Due to its noninvasiveness, medical therapy will most likely be the most commonly used initial treatment.

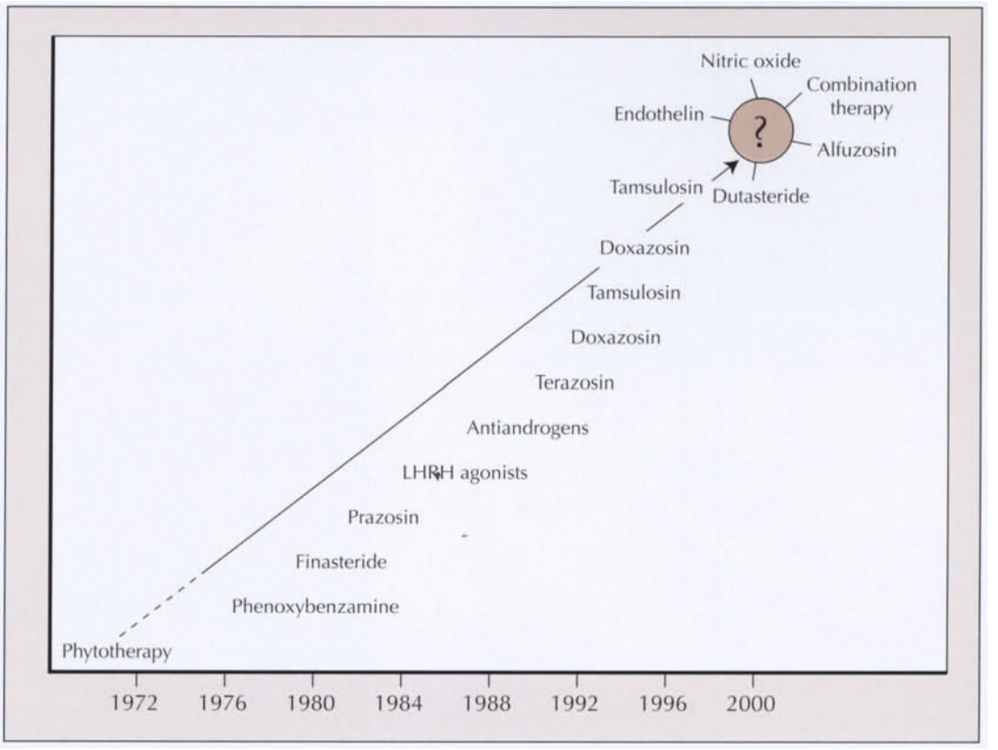


FIGURE 3-30. Timeline for the medical management of benign prostatic hyperplasia (BPH). Although medical therapy will continue to be the most commonly used treatment for symptomatic BPH, future strategies for the medical management of BPH are evolving.

The ideal agent will produce symptomatic relief of both irritative and obstructive voiding symptoms of long duration without tachyphylaxis, allow for once-daily dosing to increase compliance, have a rapid onset of action, be prostate specific and have minimal side effects, increase maximum flow rates while lowering voiding pressures, and halt the progression of BPH. As we learn more about the pathophysiology of BPH, it is hoped that more specific treatments will emerge. LHRH—luteinizing hormone–releasing hormone.

RECENT RESULTS FROM THE MEDICAL THERAPY OF PROSTATIC SYMPTOMS (MTOPS) STUDY

Outline of the MTOPS Study

Sponsor: NIH-NIDDK
Goal of study: to evaluate drug therapy in preventing progression of BPH
Method: included 3047 men; double-blind, placebo-controlled
Four-way randomization: placebo, doxazosin, finasteride, and combination

FIGURE 3-31. Outline of the MTOPS clinical research study. The aim of MTOPS is to discover whether the oral drugs finasteride and doxazosin, alone or together, can delay or prevent further prostate growth in patients with benign prostatic hyperplasia (BPH). NIDDK—National Institute of Diabetes and Digestive and Kidney Diseases; NIH—National Institutes of Health.

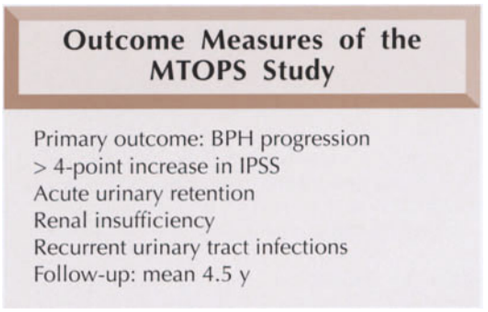


FIGURE 3-32. Outcome measures of the MTOPS study. BPH—benign prostatic hyperplasia; IPSS—International Prostate Symptom Score.

Results of the MTOPS Study

	Progression	*AUR*	*Improvement in IPSS*	*Improvement in Qmax, mL/s*
Placebo	4.5	0.6	4.0	1.4
Doxazosin	2.7	0.4	6.0	2.5
Finasteride	2.9	0.2	5.0	2.2
Combination	1.5	0.1	7.0	3.7

**Risk per 100 patient years.*

FIGURE 3-33. Results from the MTOPS study as of May 2002 [92]. AUR—acute urinary retention; IPSS—International Prostate Symptom Score; Q_{max}—maximum urine flow.

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Minimally Invasive Therapies for Benign Prostatic Hyperplasia: Transurethral Microwave Thermotherapy and Needle Ablation

4

Reginald C. Bruskewitz

Approximately 50% of all men will eventually develop lower urinary tract symptoms (LUTS), the clinical hallmark of benign prostatic hyperplasia (BPH), and will require some form of medical or surgical intervention during their lifetime [1,2]. Transurethral resection of the prostate (TURP), introduced more than 50 years ago, is still the standard treatment of BPH against which other treatments are compared [3]. However, many medical and minimally invasive treatments for LUTS and BPH have been developed and investigated in the past 10 years, effectively competing with TURP in the treatment of men with BPH. There are many reasons for the desire on the part of both patients and physicians to develop therapeutic alternatives to TURP. Aside from the obvious hesitation on the part of patients to undergo a surgical procedure in general, there are well known and described risks associated with a TURP, which are summarized in the Agency for Health Care Policy and Research guidelines for the diagnosis and treatment of BPH [4]. A careful analysis of long-term outcome data further revealed that even the presumably definite TURP procedure has a sizable re-treatment rate over time, for which various estimates are available. The best estimate reports a rate of approximately 10% over 5 years of follow-up (2% per year) compared with a significantly lower rate of 2% over 5 years following open enucleation of the prostate [4]. An additional incentive for the development of treatment alternatives is the aging of the population, with more and more older men seeking therapy who have more comorbidities and higher anesthetic risks, making them an ideal target for medical and less or minimally invasive therapies.

The use of heat to treat diseases is a very old method originally described in Egyptian papyrus scrolls. The application of heat to the prostate has been described in the form of hot water perfusion of the urethra, galvanocautery (Newman, 1886), heat-induced shrinkage (Kirwin, 1932), and prostatic desiccation (Mebust, 1977). The modern era of heat treatment for benign enlargement of the prostate was ushered in by the use of first rigid [5] and then flexible [6] microwave antennae placed in proximity of the prostatic adenoma.

Since then, at least three distinct heat-based therapies for BPH have emerged clinically: transurethral microwave thermotherapy (TUMT) [7], water-induced thermotherapy, and transurethral needle ablation of the prostate (TUNA) [8–12]. The available basic science and clinical assumptions underlying heat therapy for BPH are reviewed, as well as the physical principles of the different technologies and their clinical results. This chapter focuses on TUMT and TUNA.

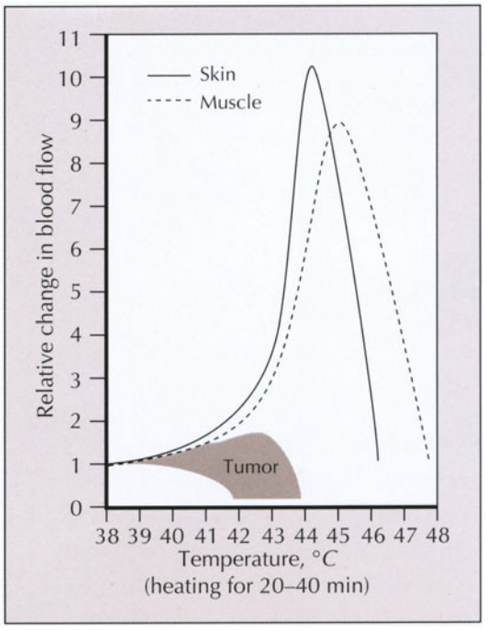


FIGURE 4-1. Comparison of blood flow due to vasodilation in normal tissue versus that in tumor tissue. It has long been recognized that malignant cells are more susceptible to heat than normal tissue. Part of this reaction is due to the type of vascularity found in malignant tissue, which provides high resistance to blood flow and poor response to heat with vasodilation as is the case in normal tissue. In addition, hypoxic cells, often found in tumor cells, are particularly sensitive to heat destruction. Lastly, it was theorized that the use of local hyperthermia to cancers may enhance the immunologic response to a tumor. This figure illustrates how skin and muscle tissue exhibit a tremendous increase in blood flow due to vasodilation, while tumor tissue demonstrates little to no change in blood flow. For this reason, early efforts at hyperthermia were directed toward prostate malignancies, and many reports have been published using transurethral microwave hyperthermia for the treatment of prostate cancer [13].

Effect of Heat on Normal Prostate Tissue

Temperature	*Tissue Effect*	*Therapy*
37°	None	Fever
42° to 44°	No histologic changes	Hyperthermia
45° to 50°	Minimal changes	Thermotherapy
60°	Protein denaturization	Thermocoagulation
100° +	Coagulation and vaporization	Thermoablation

FIGURE 4-2. Effect of heat on normal prostate tissue. By convention, hyperthermia is defined as raising tissue temperature from 42°C to 44°C. Whereas at this temperature normal tissue does not exhibit any histologic changes, malignant tissues are susceptible to this level of heat. At temperatures above 45°C, both malignant and normal cells are affected by heat, and cell death may occur. Temperatures of higher than 60°C induce protein denaturation (thermocoagulation), and temperatures higher than 100°C induce coagulation and ultimately vaporization of tissue (thermoablation). It is thus apparent that any treatment aiming at tissue ablation in the prostate should strive to achieve temperatures higher than 45°C—a theoretical observation that was proven correct by the ineffectiveness of those treatments that achieved temperatures of lower than 45°C.

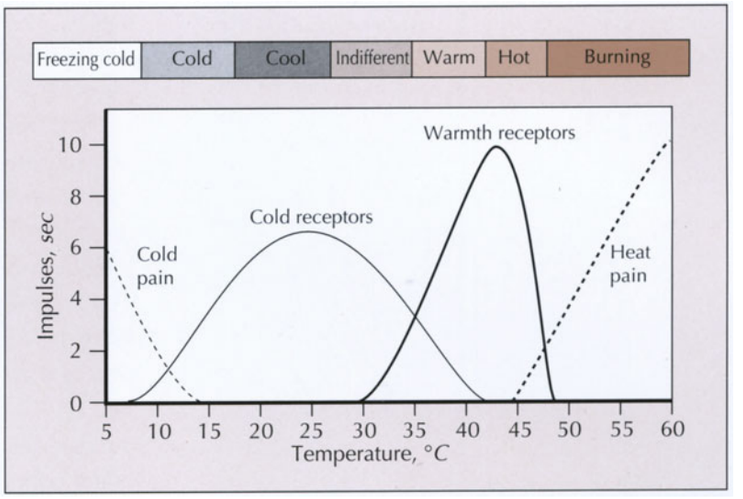


FIGURE 4-3. Frequencies of discharge of various fibers. One problem with the theoretic observation described in Figure 4-2 is the normal body response to temperature changes. While the peak discharge of cold fibers occurs at temperatures between 20°C and 30°C, warm fibers start discharging at 30°C up to approximately 50°C, and at 45°C, heat–pain fibers start discharging.

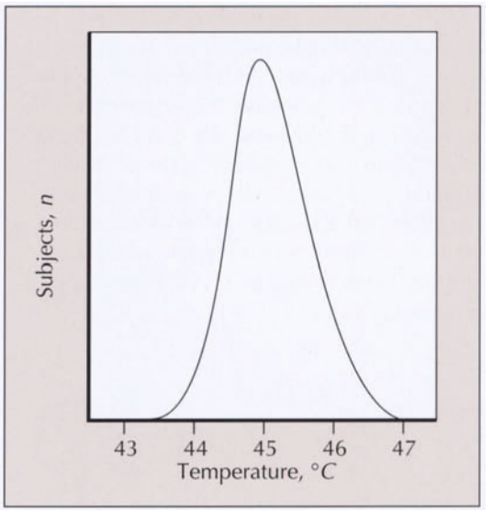


FIGURE 4-4. Distribution curve of the minimal skin temperature that causes pain. Accordingly, most normal subjects perceive pain at skin temperatures between 44°C and 46°C. Although most physiologic research done on heat receptors and pain fibers is done on tissues other than prostate and urethra, it appears logical to conclude that at about the temperature threshold needed for effective damaging of tissue, pain and heat fibers will start discharging, thus limiting the ability to administer temperature without appropriate preventive and corrective measures.

Biologic Effects of Various Wave Frequencies

Frequency, Hz	*Spectrum*	*Biologic Effects*
10^2 / 10^4	Audio frequency Power transmission Telephone	Ventricular fibrillation Convulsions
10^6 / 10^8	Commercial and short-wave radio waves	No effect except by direct contact
10^{10} / 10^{12}	Microwave Radar Diathermy	Molecular excitation Tissue heating
10^{14}	Infrared, cooking, heating, lasers, photography	
10^{14} / 10^{16}		Molecular disruption Sunburn, tanning, cancer Photoreactions
10^{16}	Light: ultraviolet, spectroscopy	
10^{16} / 10^{18}		Atomic and molecular ionization
10^{18} / 10^{20} / 10^{22}	Ionizing radiation	Nuclear interactions

FIGURE 4-5. Biologic effects of various wave frequencies. Waves with a frequency of less than 10^8 Hz or 100 MHz (*eg*, telephone, commercial, and short-wave radio waves) do not cause any biologic effects. Microwave energy, radar, and diathermy cause molecular excitation and radiative tissue heating. Waves with frequencies above this level cause various biologic effects, ranging from molecular disruption (sunburn, photo reactions, cancer) to atomic and molecular ionization, and, ultimately, nuclear interactions (ionizing radiation for diagnostic and therapeutic purposes).

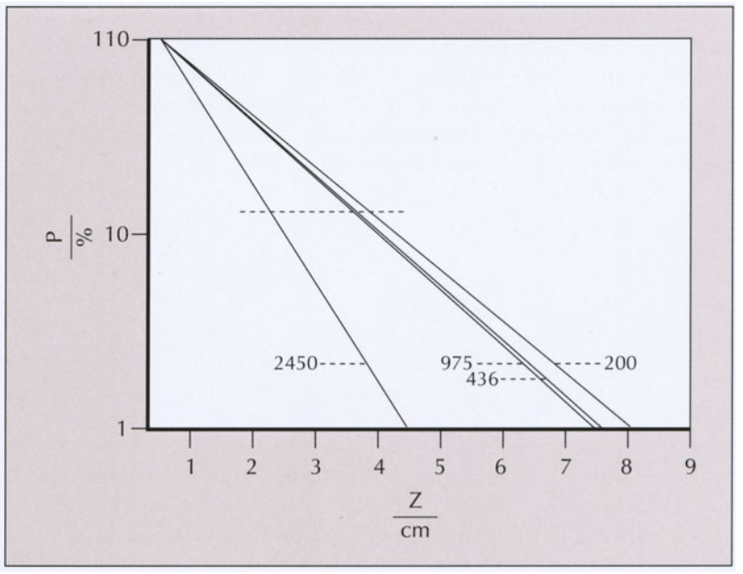


FIGURE 4-6. Frequency dependence of penetration into muscle from 10 cm × 10 cm aperture. Radiative heating by microwave energy can be conducted with a number of applicators ranging in frequency from 434 to 2450 MHz. However, the depth of tissue penetration is inversely correlated to the frequency of the wave length: the higher the wave length, the less penetration can be achieved. Individual variations in the anatomies, such as blood supply of the urethra, the rectum, the prostate, and variations in prostate morphology affect radiative heatings. Energies are delivered to the tissue by conductive, convective, and absorptive mechanisms; the exact mechanisms of microwave energy treatment of the prostate is, however, extrapolated from oncology data.

TRANSURETHRAL MICROWAVE THERMOTHERAPY

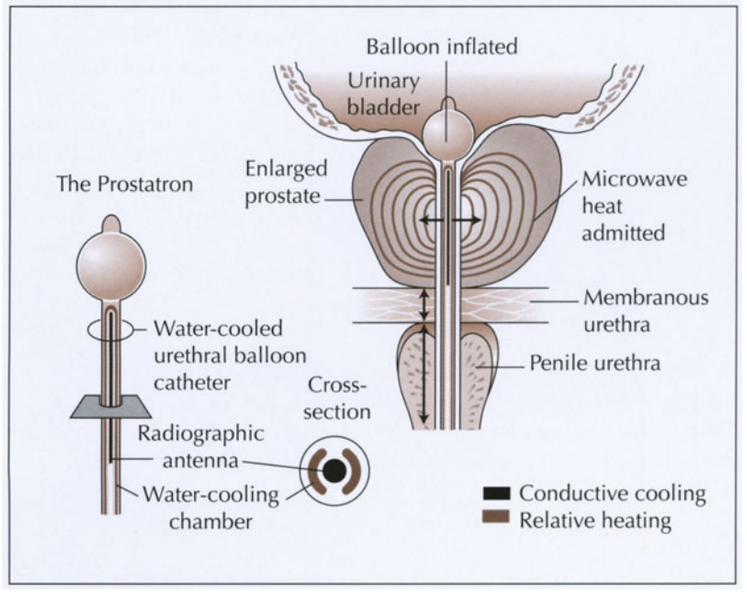


FIGURE 4-7. Transurethral microwave thermotherapy (TUMT) refers to the heating of the prostate in excess of 45°C, thus inducing noticeable histologic changes. The energy and temperature associated with TUMT incurs two problems: 1) the increased temperature has the potential of inducing necrosis of the urethral lining, which would result in tissue sloughing with unpleasant and bothersome irritative symptoms following treatment; and 2) temperatures in excess of 45°C induce pain sensation in most patients (see Figs. 4-3 and 4-4) and, accordingly, would require anesthetic provisions.

A cooling system has been developed (Edap Technomed, Cambridge, MA) that is currently in use in commercially available TUMT devices. The microwave antennae placed in the prostatic urethra is surrounded by a second chamber that is perfused with prechilled water. The configuration of the balloon (*eg*, completely circumferential, only lateral, mostly posterior) as well as the temperature of the prechilled fluid with which the system is perfused varies from device to device. The fundamental principal, however, is the same: the cooling of the immediate urethral lining and the first few millimeters of periurethral tissue prevents both necrosis and tissue sloughing as well as pain sensation in the patient.

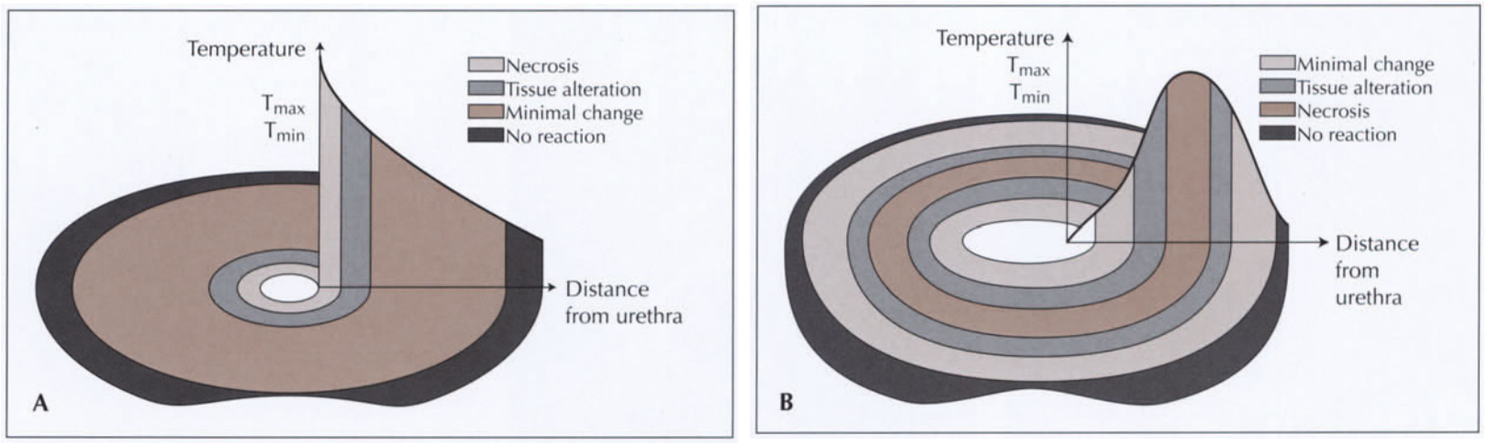


FIGURE 4-8. Urethral heating with and without cooling. **A,** Urethral heating without cooling leads in the peak temperature being measurable in the immediate periurethral tissue with a sharp radial temperature drop-off away from the energy source. **B,** Urethral heating with cooling protects the urethral lining and the immediate periurethral tissue. The peak temperature is achieved deeper within the prostate, namely in the periurethral glandular tissue, which is the primary target on any minimally invasive treatment modality.

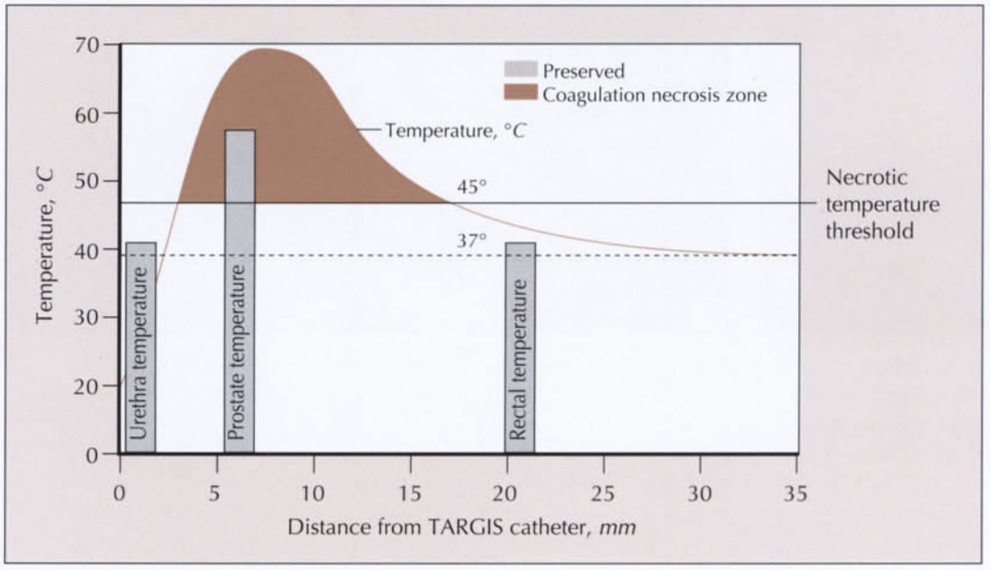


FIGURE 4-9. Microwave treatment of the prostate. While using different frequencies ranging from 95 to 1296 MHz, extensive interstitial temperature mapping studies performed with all commercially available devices have demonstrated that temperature in excess of 45°C can be achieved. The actual distribution of temperatures differs considerably, presumably depending on anatomy and histologic composition. Careful mapping studies with the TARGIS (Urologix, Minneapolis, MN) device demonstrates effective temperatures within the prostate from about 3 to 15 mm away from the urethra. Cooling provides adequate protection of the urethral lining, and peripheral prostate tissue, rectal wall, and tissue outside the prostate remains at body temperature.

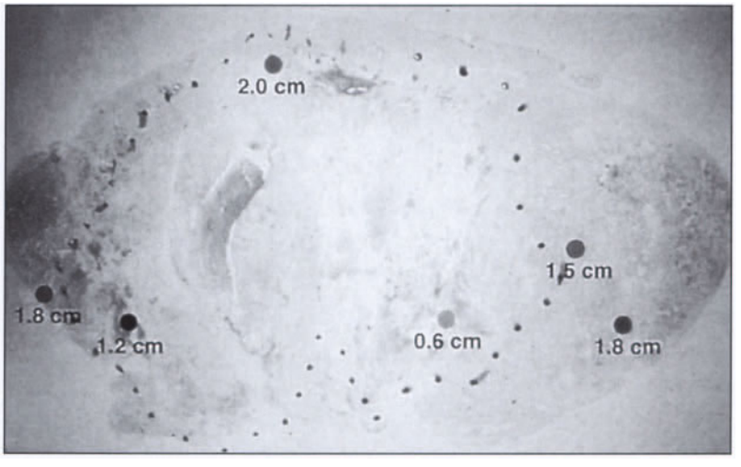


FIGURE 4-10. ***(See Color Plate)*** Interstitial pathology specimen following TARGIS (Urologix, Minneapolis, MN) therapy. In this whole-mount histologic section, the interstitial thermometry measurements are indicated by their distance from the antennae in the urethra. The *dotted line* indicates the area of necrosis induced, which is roughly an area 1.5 to 2.0 cm circumferentially around the urethra.

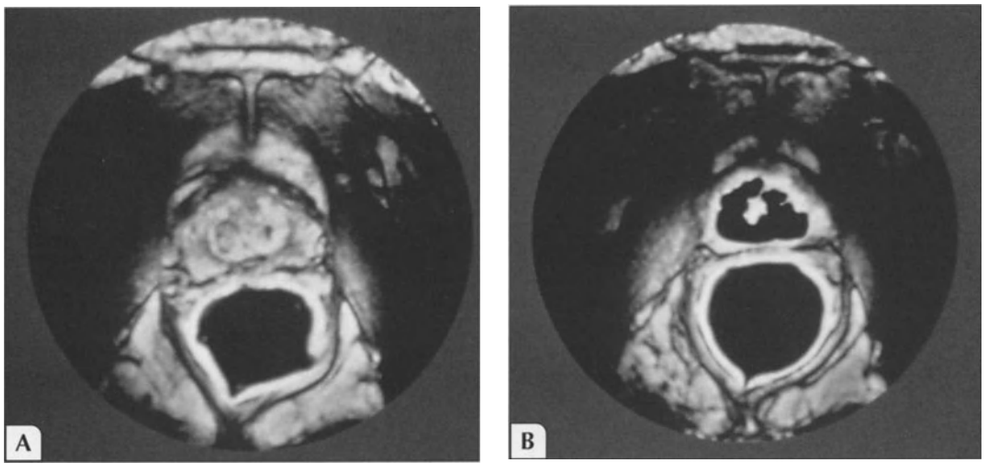


FIGURE 4-11. Prostatic tissue necrosis. T_2-weighted, fat-suppressed, gadolinium-enhanced pelvic magnetic resonance imaging (MRI) has provided visual evidence of necrosis induced in the prostate. These MRI images obtained before (**A**) and after (**B**) transurethral microwave thermotherapy (TARGIS; Urologix, Minneapolis, MN) indicate a necrotic area in the prostate circumferentially surrounding the urethra.

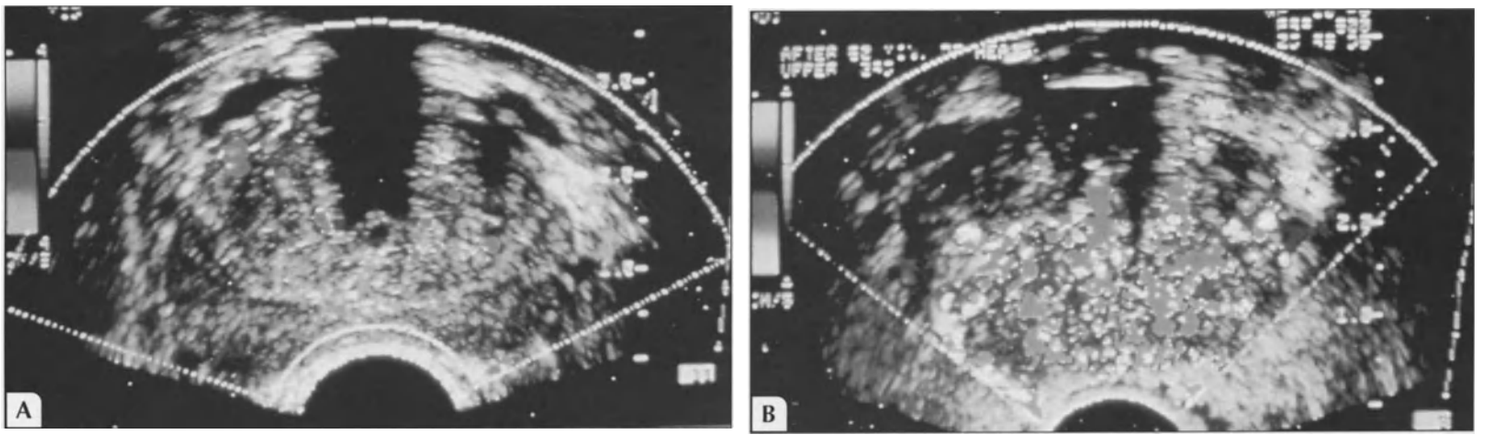


FIGURE 4-12. ***(See Color Plate)*** Color Doppler–enhanced transrectal ultrasonography has also proven useful in the assessment of the treatment efficacy of transurethral microwave thermotherapy. **A,** Prior to therapy, there is very little blood flow in the peripheral and transition zone of the prostate. **B,** However, after approximately 40 minutes of treatment, an enormous increase in blood flow pattern in the peripheral and transition zone of the prostate is noted. This blood flow is mostly due to heat-induced vasodilation (see earlier discussion). Initially, the heat-induced vasodilation distributes the heat in the prostate by convection and, ultimately, causes a loss of energy by carrying the heat away via venous outflow from the prostate. Later in the treatment, however, small blood vessels become obliterated, making the prostate in essence a "heat sink." It is at those time points that in general the requirement of additional energy input to maintain therapeutic temperature decreases, while ongoing tissue damage occurs.

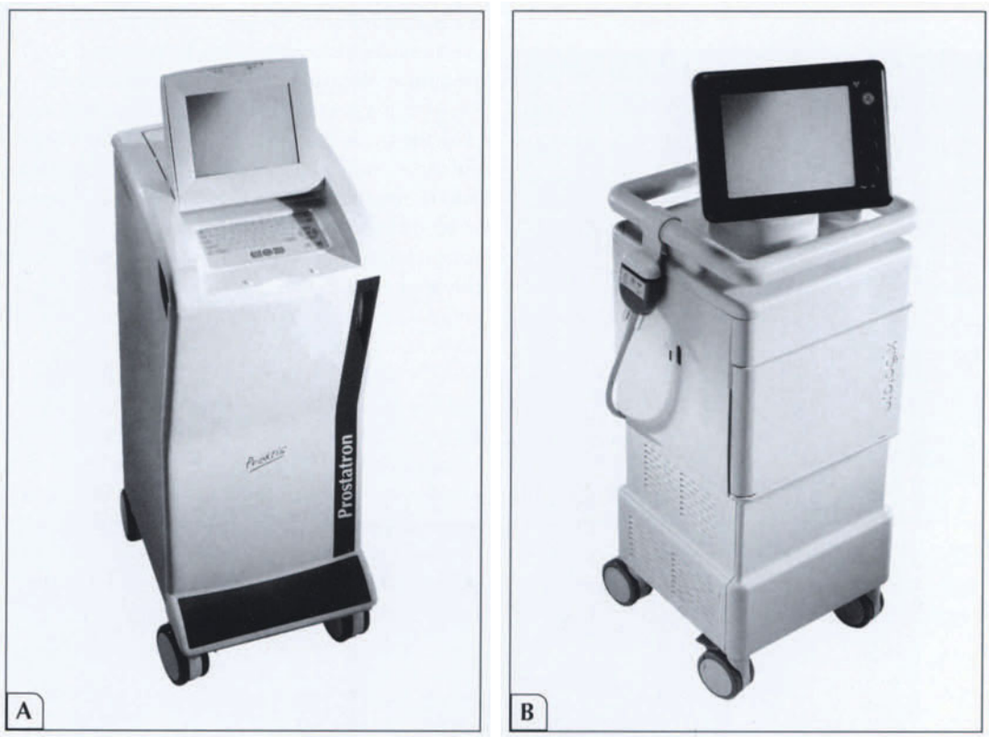


FIGURE 4-13. Devices used for transurethral microwave thermotherapy. Although the available equipment differs in the external appearance, all devices have a microwave power generator, a keyboard for pertinent data entry, and a computer screen to display in real-time treatment parameters, adjust temperatures, energies, coolant flow, and so on. **A,** The Prostatron. **B,** The TARGIS T3 (Urologix, Minneapolis, MN).

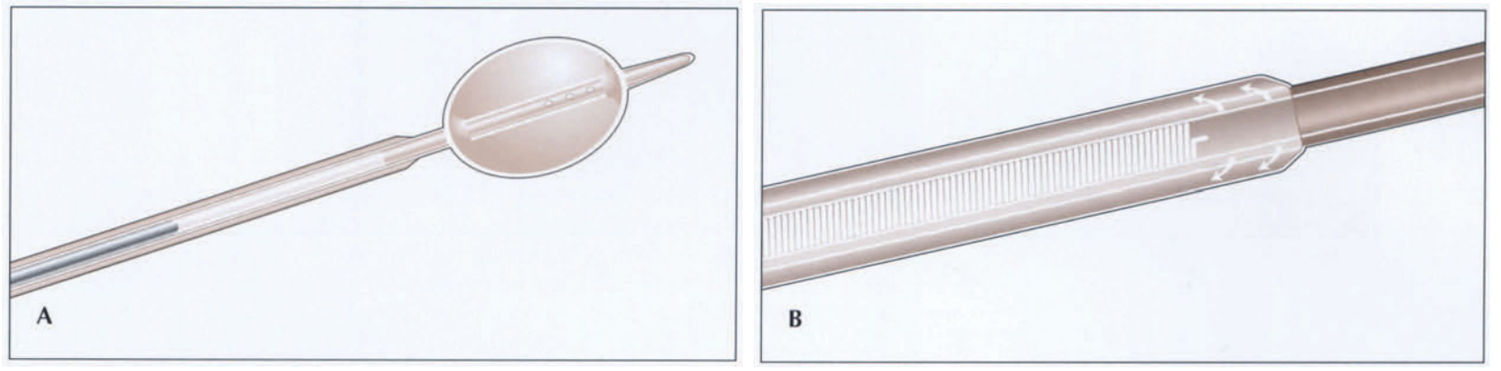


FIGURE 4-14. Treatment catheters. The disposable part of the system, the treatment catheter, also varies from device to device. Fundamentally, however, all commercially available and currently used devices employ a catheter featuring an anchoring balloon (**A**) to secure the catheter firmly at the bladder neck, usually verified by transabdominal or transrectal ultrasonography. Furthermore, they feature an antennae that is surrounded by a chamber allowing perfusion with prechilled water for urethral cooling (**B**). The configuration of the cooling chamber, the temperature of the water, and the intensity of water flow during treatment varies from device to device. In addition to these elements, most catheters also feature a central channel to drain the urine during the actual treatment. (*Courtesy of* Dornier Med Tech, Kennesaw, GA.)

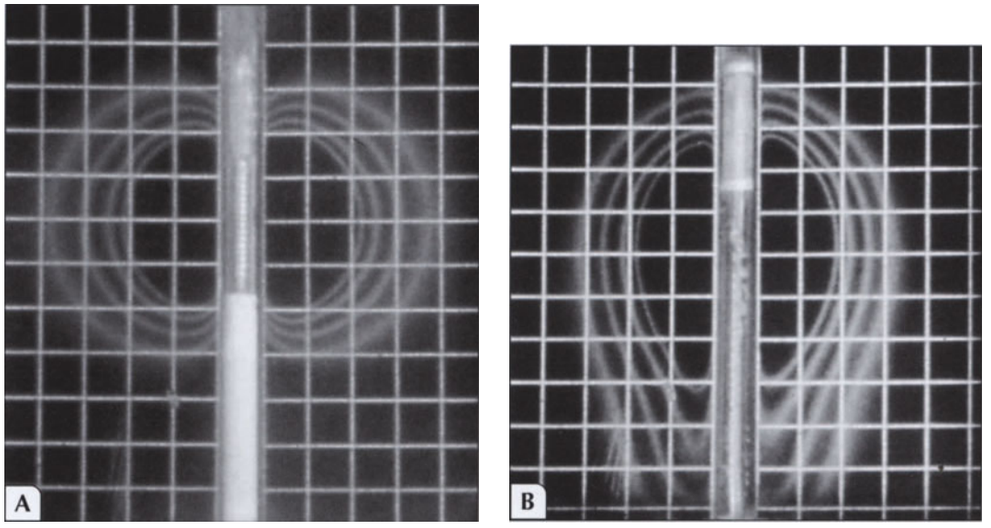


FIGURE 4-15. Energy transmission patterns. **A,** TARGIS. **B,** Prostatron (Urologix, Minneapolis, MN). The most complex part of the energy delivery unit is the microwave antennae. The problem with delivering microwave energy into the prostate is in achieving the appropriate and optimized configuration of the antennae. Impedance (see previous discussion) often leads to a significant amount of the energy being reflected rather than entering the prostate. Thus, calculation of delivered energy by the treatment console often overestimates the actual energy and heat transmitted into the prostate proper. These antennae demonstrate different energy transmission patterns in heat-sensitive materials. The TARGIS antennae feature a strict dipole configuration with a circular heating pattern around the antennae. The two antenna features a monopole design with "leakage" of energy along the shaft of the catheter into the area of the external urinary sphincter. Whether these design differences translate into actual clinical differences in terms of patient outcomes is uncertain. However, it is noticeable that despite the apparent energy leak proximal to the antenna with the theoretical risk of external sphincter damage, urinary incontinence is rarely reported.

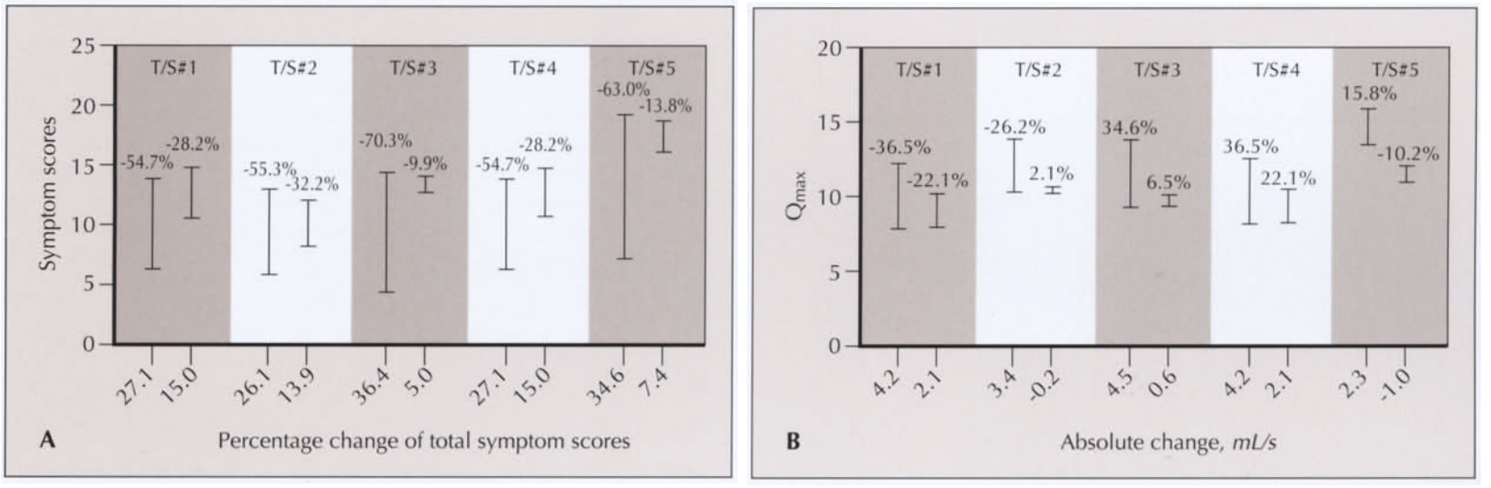


FIGURE 4-16. Pre- and posttreatment symptom scores (**A**) and peak urinary flow rate (**B**) for five sham-controlled transurethral microwave thermotherapy trials. The *top of the bar* indicates the pretreatment symptom score; the *bottom of the bar* indicates the posttreatment symptom score (vice versa for the peak urinary flow rate). The *first vertical bar* for each trial indicates the active treatment group; the *second vertical bar* indicates the sham treatment group. Percentage reduction is indicated on top (bottom for peak flow rate) of the bars and the percent change of the total symptom score and the absolute change (in milliliters per second) along the X axis. Two observations are pertinent. In all trials, the active treatment group was significantly superior in terms of symptom and reduction in flow rate improvement compared with the sham treatment group arm. Secondly, in all studies there was a response to the sham treatment both in terms of symptom and peak urinary flow rate with the exception of the fifth trial, in which a 10% decrease in peak flow rate occurred (**B**). Thus, it appears that transurethral microwave thermotherapy provides symptomatic and flow rate improvement above and beyond that achieved by simple placebo or sham treatment, or by the 1-hour catheterization associated with the sham therapy [14].

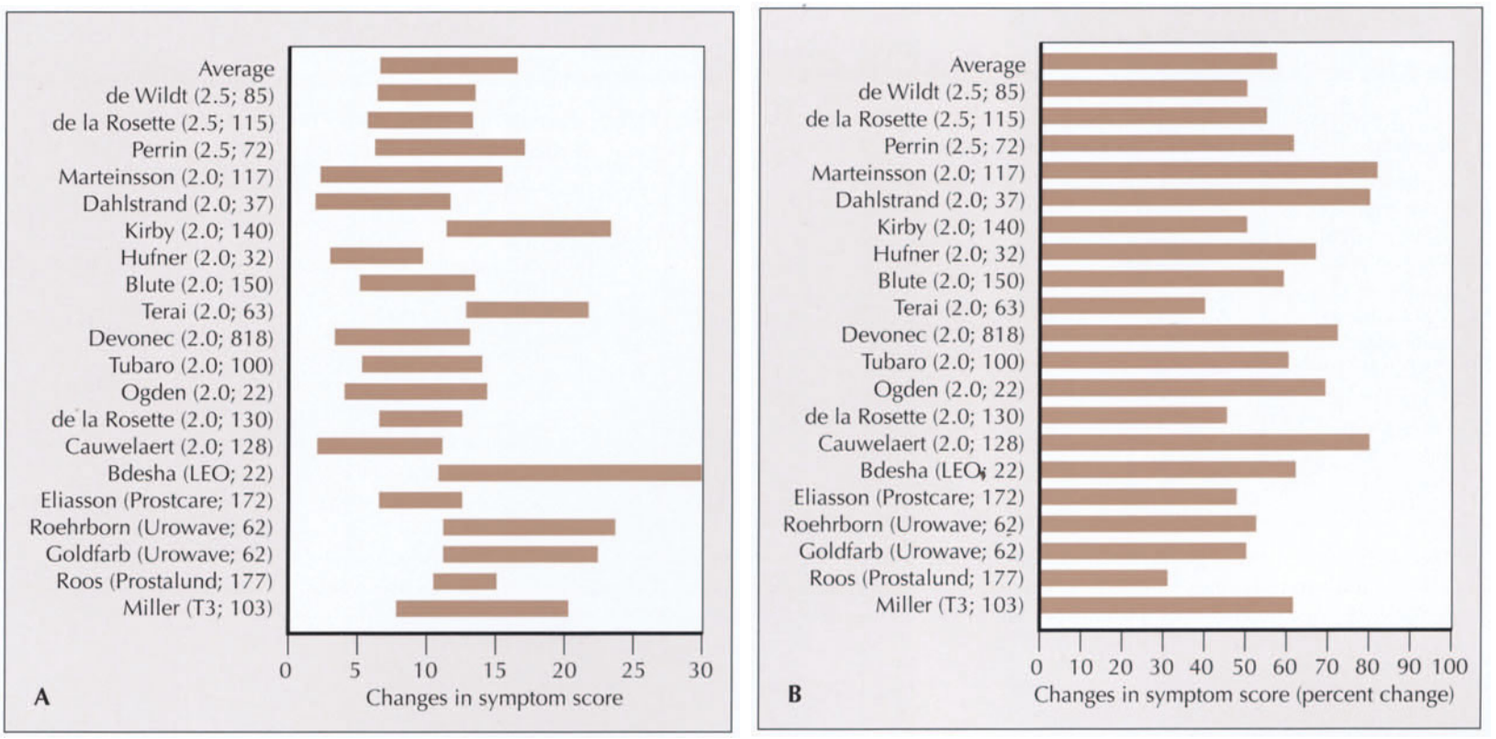


FIGURE 4-17. A summary of studies conducted with either the Prostatron (EDAP Technomed, Cambridge, MA) 2.0 software, the Prostatron 2.5 software, or other devices such as the Leo Prostatherma, the ProstaCare device, the Urowave (Dornier Med Tech, Kennesaw, GA), or the TARGIS T3 (Urologix, Minneapolis, MN) device. The numbers in parentheses indicate the number of patients in the study. The abundance of clinical data published in the peer-reviewed literature has been summarized by de la Rosette *et al.* [7]. **A,** The changes in symptom score are shown along the X axis. The *right side* of the bar illustrates the pretreatment symptom score; the *left side* of the bar, the posttreatment symptom score. It is evident that all devices reduce the symptom score considerably; however, the pretreatment symptom severity was very different from trial to trial. **B,** The same trials, but the symptom score improvement is expressed as a percent change. It is evident that on average, a 60% symptom score reduction was achieved with a range of 30% to 80%.

Morbidity After Treatment

Study*	Patients, n	Catheterization	Retention, %	Hematuria, %	UTIs, %	Ejaculation Problem, %	Stricture, %	Incontinence, %	Re-treated, %
Miller *et al.*	103	—	—	—	—	—	—	—	—
Roos and Pedersen	177	—	3.3	2.2	2.3	—	0.0	0.0	9.0
Goldfarb *et al.*	62	—	4.8	12.9	0.0	3.2	0.0	0.0	—
Eliasson *et al.*	172	—	6.0	62.0	2.3	0.0	—	0.0	1.1
Bdesha *et al.*	22	—	—	31.8	—	0.0	—	—	—
Van Cauweaert *et al.*	128	3.1 d	33.0	2.6	—	0.0	—	—	0.6
de la Rosette *et al.*	130	—	26.0	4.5	—	0.8	0.0	0.0	10.7
Ogden *et al.*	22	—	22.0	—	—	—	—	—	4.5
Tubaro *et al.*	100	—	—	—	—	—	—	—	—
Devonec *et al.*	818	—	10 to 40	—	—	0.0	—	—	7.0
Terai *et al.*	63	3.9 d	36.0	1.5	1.5	1.5	—	—	—
Blute *et al.*	150	—	36.0	40.0	—	†0.6	—	—	—
Hofner *et al.*	32	—	—	—	—	—	—	—	—
Kirby *et al.*	140	—	25.0	†	15.0†	—	—	—	3.0
Dahlstrand *et al.*	37	1 to 7 d	13.5	0.0	13.5	—	—	—	10.8
Marteinsson and Due	115	14.8 d	28.6	—	6.9	1.7	—	—	—
Netto *et al.*	100	—	—	—	—	11.0	—	—	—
Perrin *et al.*	72	> 2 wk	80.0	—	—	—	—	—	—
de la Rosette *et al.*	116	16 d	100.0	76.0	7.0	44.0	0.0	0.0	5.9
de Wildt *et al.*	85	14.3 d	100.0	—	—	33.0	—	—	2.6

*For complete reference information, see Gibbons et al. [15].
†Hematuria and infections.

FIGURE 4-18. Morbidity after treatment. Adverse events in general have been temporary, mild, and comparable between the different treatment modalities. Urinary incontinence and erectile dysfunction have not been a significant problem with any of the devices; hemospermia and other ejaculatory problems have occurred with varying frequency. The higher intensity devices appear to induce more hemospermia and occasionally other ejaculatory dysfunctions. Since the publication of this table, several individual cases of urethral stricture formation in the prostatic urethra have been reported. These, however, have remained isolated cases. Intermittent hematuria is reported by a significant number of patients, but it is of no clinical consequence because it is not associated with clot formation or clot retention. A considerable problem in the analysis and comparison of data is the issue of retention following treatment. In most research protocols, the protocol specifically instructed physicians to place a Foley catheter or a suprapubic catheter for a specified period of time. Thus, if every patient in a given trial by protocol has to have an indwelling catheter for at least 5 days, the average duration of catheterization can only be 5 days or greater. In other studies, voiding trials were allowed as early as on the first postoperative day. Thus, because the days of catheter requirement vary greatly, caution is advised when interpreting such data. The only way to determine whether or not differences exist between different modalities would be to have a direct comparison of different devices in which each patient is given a voiding trial every 24 hours until he is able to empty his bladder with reasonable residual urines. The issue of re-treatments is of great concern. Treatment failure and subsequent re-treatment with another invasive modality incurs considerable cost and is a disadvantage for any minimally invasive treatment. In this context, it is relevant to note that re-treatment dates have been reported very inconsistently. UTLs—urinary tract infections. (*Adapted from* Gibbons *et al.* [15].)

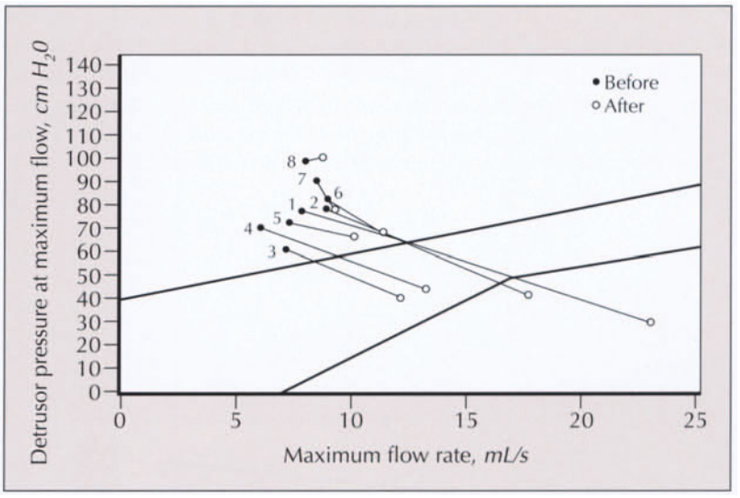


FIGURE 4-19. The urodynamic effects of various treatment modalities for benign prostatic hyperplasia [17]. The figure shows the average effect of open prostatectomy (line 1), transurethral resection (TURP) (line 2), transurethral incision (TUIP) (line 3), laser prostatectomy (line 4), transurethral microwave thermotherapy (TUMT) (line 5), α-blocker treatment (line 6), androgen deprivation (line 7), and placebo (line 8) on the P_{det} (detrusor pressure) at Q_{max} and the peak urinary flow rate plotted on the Abrams-Griffith nomogram. Whereas all surgical modalities (lines 1 through 4) on average transfer the patient population from an obstructed to an unobstructed or at least equivocal state, none of the other treatment modalities does so. Specific to TUMT, there is improvement in peak urinary flow rate with only a minor reduction in the P_{det} at Q_{max}. Without doubt, one of the most important research agenda items in the area of TUMT is currently to determine which patients are ideally suited candidates for this form of therapy. It is very evident that there are some patients who have an excellent symptomatic and occasionally also flow rate improvement, whereas there are other patients who have no improvement at all or actually worsening of their symptoms. Ability to predict such response prior to treatment discussion would greatly help in reducing the number of re-treatments [18].

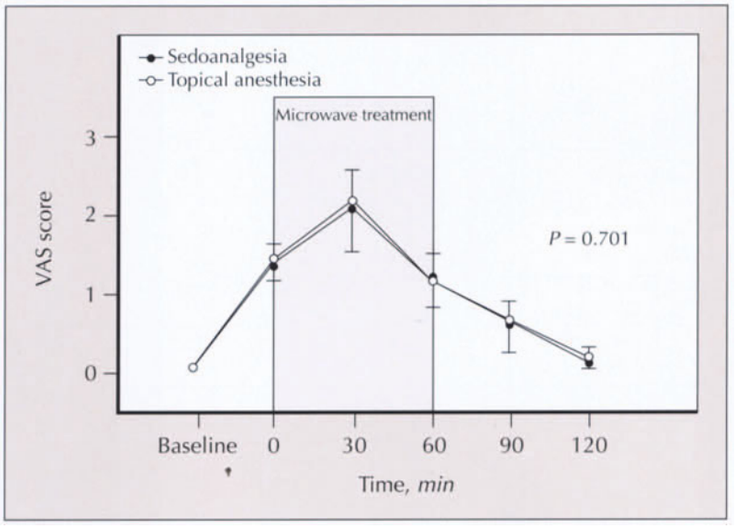


FIGURE 4-20. Mean visual analog scale (VAS) scores with 95% CI before, during, and after transurethral microwave thermotherapy (TUMT). Although anesthetic requirements reported differ from trial to trial, it is evident that all TUMT treatments may be performed in an office setting. In most cases, topical intraurethral anesthesia is used, augmented with a variety of analgesic or anesthetic medications, given either orally, intramuscularly, or intravenously. In this context, a recent study by Djavan *et al.* [19] is of considerable interest. Forty-five patients were treated with high-energy TUMT and randomly assigned to receive either topical intraurethral anesthesia alone or topical anesthesia with adjunctive intravenous sedoanalgesia. The treatment was delivered with the TARGIS T3 (Urologix, Minneapolis, MN) device. Patients were given a VAS before, during, and after treatment, and as is evident from the figure shown, the perception of pain was very similar between the two groups with no significant differences occurring at any time point either during or after the treatment. Although individual patients may vary in their perception of pain, overall the principal of urethral cooling has resulted in the TUMT treatment being fundamentally an outpatient, office-based therapy with no need for anesthesia services. What is currently needed is longer follow-up with more precise definition of re-treatment rates, and further research into predictors of response.

TRANSURETHRAL NEEDLE ABLATION

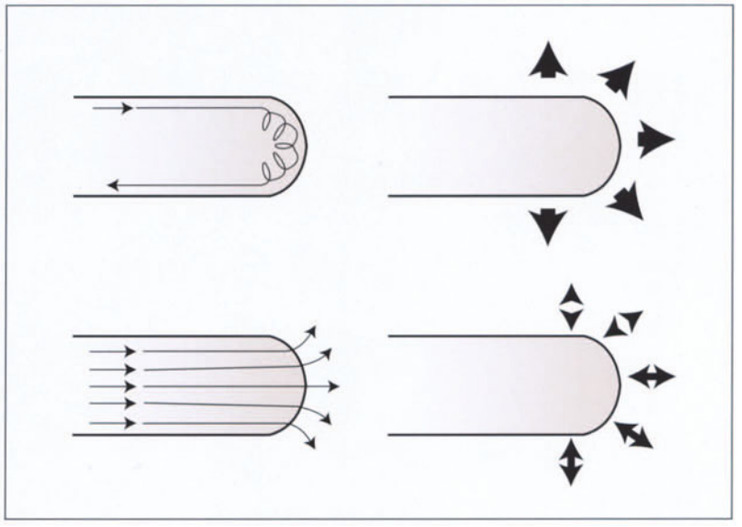


FIGURE 4-21. Principles of radiofrequency (RF) energy. Transurethral needle ablation uses low-level RF generator operating frequency of 415 KHz, which is delivered under visual control into specific prostatic areas by means of endoscopic needle placements. In contrast to resistive heating (*top*), RF is delivered to the tissue without the needles actually getting hot themselves. The frequency of the RF waves causes this agitation of the tissue particles and ions. This produces friction and creates heating of tissue. The tissue itself then becomes the conductor of the heat, not the needles.

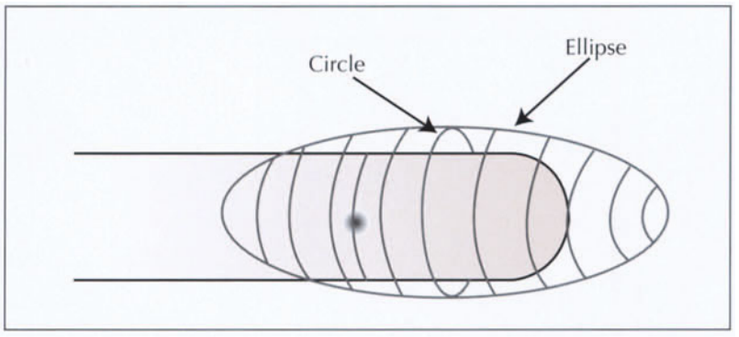


FIGURE 4-22. The radiofrequency (RF) lesion. As with other sources of energy, a feature of RF energy is a steep thermal gradient that is created when RF waves are delivered interstitially. The tissue immediately adjacent to the needle tip is heated to temperatures as high as 100°C, and then the temperature falls off, quickly reaching body temperature within 1 to 2 cm. The resulting lesion size is elliptic in shape, centered around the exposed needle electrode.

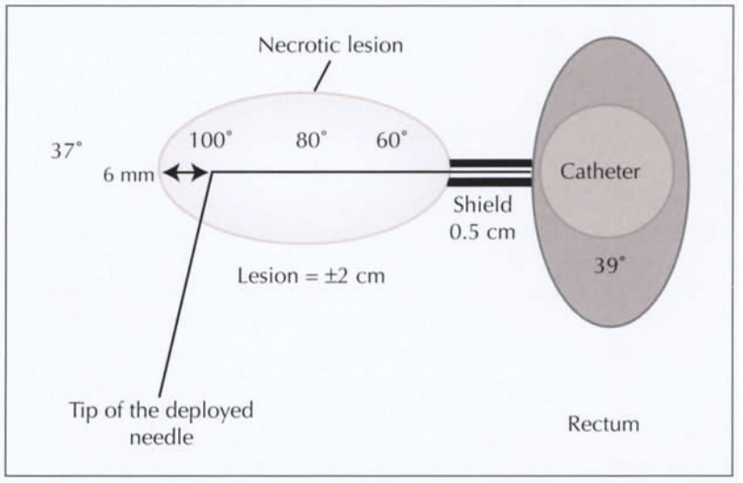


FIGURE 4-23. Temperature distribution and lesion size with transurethral needle ablation. By shielding the exposed needle immediately adjacent to the urethra with a polytef sheath, the elliptical shape necrotic lesion is positioned in the periurethral gland with the urethral lining itself remaining at body temperatures without need for water cooling, and thereby eliminating tissue sloughing.

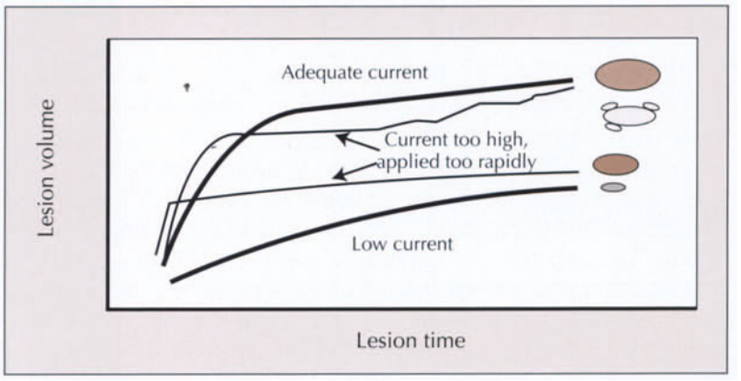


FIGURE 4-24. The resulting lesion size is a function of the energy delivered over time. The automated radiofrequency generator is programmed to achieve the best possible result. This is partially done by monitoring impedance in the tissue. Impedance is the resistance to the flow of current in the tissue that increases as tissue is desiccated and current flow is restricted. By continually monitoring impedance, optimalization of the lesion volume is achieved.

FIGURE 4-25. The transurethral needle ablation (TUNA) system. The TUNA system consists of a radiofrequency generator with an integrated keyboard for data entry, which allows for simultaneous monitoring of urethral, prostatic, and rectal temperatures in real time.

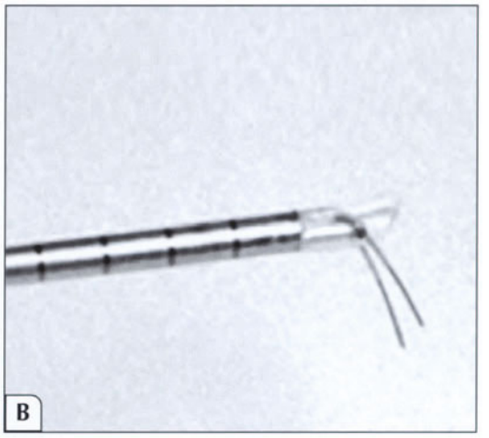
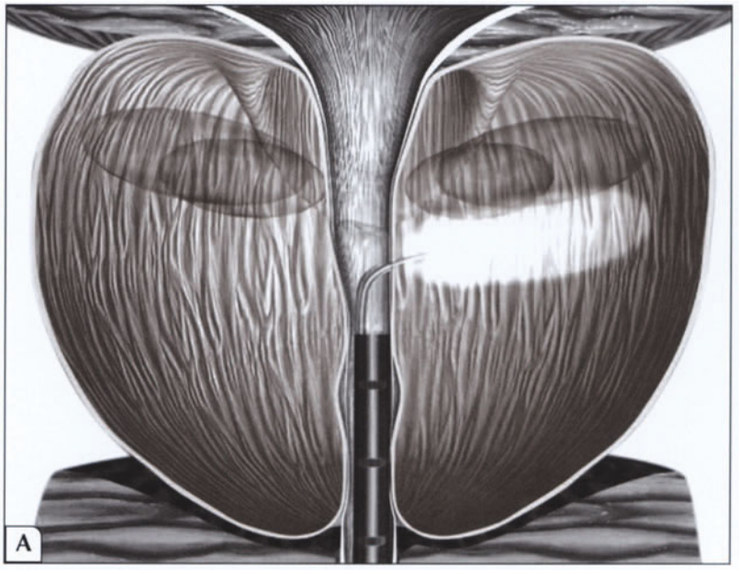


FIGURE 4-26. Hand piece of the transurethral needle ablation system. **A,** The hand piece consists of the treatment catheter with the needles, and accepts a 0μ optical lens. Integrated thermocouples monitor urethral temperature to prevent urethral damage. **B**, The catheter tip is clear, allowing visualization for accurate needle placement. The needle tips and the polytef shields are advanced according to the transverse diameter of the prostate assessed by transrectal ultrasonography. If the transverse measurements range from 34 to 46 mm, the exposed needle length should range from 11 to 18 mm and the shield should be advanced by 5 mm. If the transverse measurement ranges from 47 to 64 mm, the needle length should range from 18 to 22 mm with 6 mm of shielding.



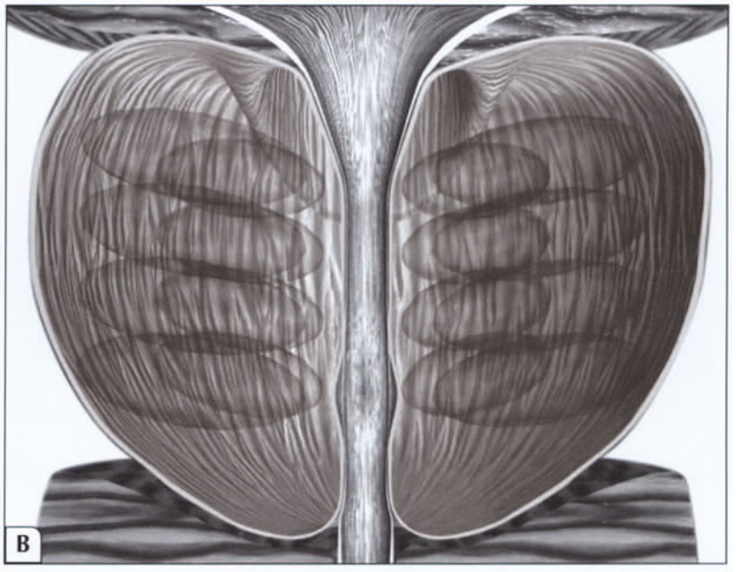


FIGURE 4-27. Sequence of the transurethral needle ablation procedure. The number of treatment planes depends on the length of the prostatic urethra as determined by transrectal ultrasonography or cystoscopy. If the distance from the bladder neck to the verumontanum is less than 4 cm, right and left treatments are administered in two planes. If the distance is 4 to 5 cm, three planes are treated, and if the distance is over 5 cm, four planes are treated. After the first treatment is administered at the bladder neck plane on the right-hand side (**A**), the orientation of the needle is changed and the contralateral site is treated. Thereafter, the next tissue plane is treated in the same fashion (**B**).

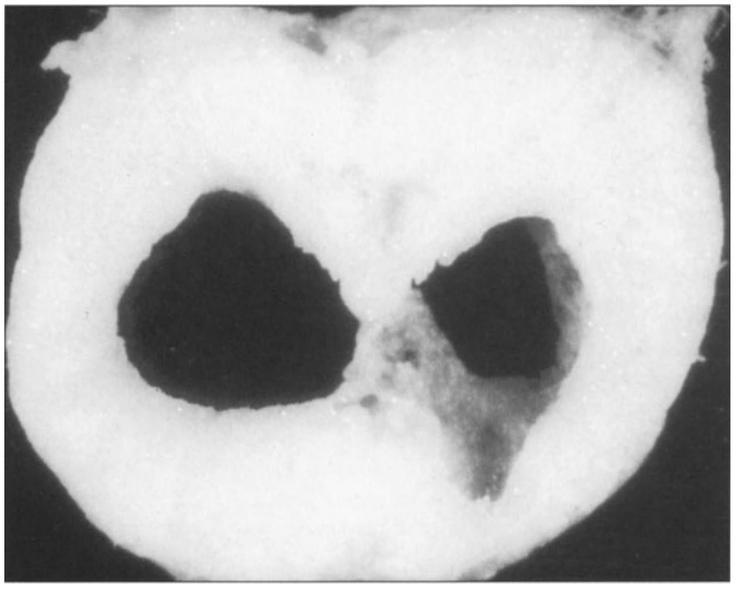


FIGURE 4-28. Prior to human treatments, animal experiments were conducted demonstrating that necrotic lesions could be created in the dog prostate using the transurethral needle ablation with no resultant damage to the rectum, bladder, external sphincter, or distal prostatic urethra [20].

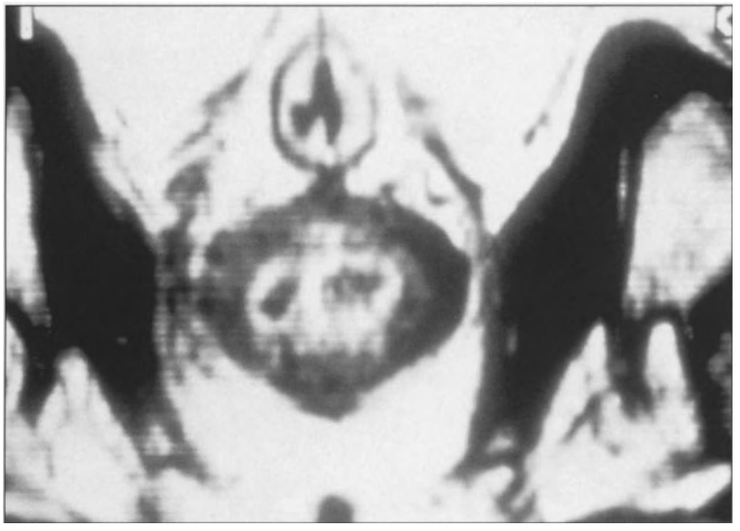


FIGURE 4-29. Gadolinium-enhanced magnetic resonance images of the pelvis demonstrate symmetrically placed necrotic lesions within the prostate following transurethral needle ablation treatment corresponding to areas of necrosis demonstrated on a cross-section of the surgically removed prostate (see Fig. 4-47) [9–11].

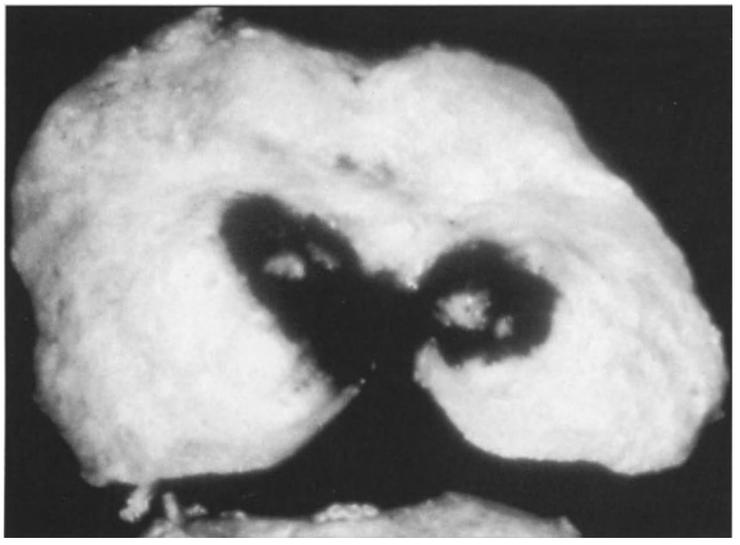


FIGURE 4-30. Cross-section of the surgically removed prostate.

Wordwide Results of Transurethral Ablation of the Prostate

Study Group*	Patients, n	Follow-up, mo	Symptom Score			Peak Flow Rate		
			Baseline	Post-TUNA†	Percent Change	Baseline	Post-TUNA†	Percent Change
US/Pilot Study (Issa *et al.*)	12	6	25.5	9.8	-61	7.8	13.5	+73
US/Multicenter Study (Roehrborn *et al.*)	130	12	23.7	11.9	-50	7.8	14.6	+68
US/Multicenter Randomized Study (Bruskewitz *et al.*)	65	12	24.7	11.1	-55	6.7	15.0	+72
Brussels, Belgium (Schulman *et al.*)	36	12	21.5	7.8	-64	9.9	16.8	+69
	25	24	21.6	8.5	-61	9.9	15.5	+57
	17	36	21.6	7.6	-65	9.9	16.2	+64
Harlow, UK (Virdi *et al.*)	71	12	22.3	10.0	-55	7.0	13.8	+97
	71	24	22.3	9.4	-58	7.0	14.8	+111
	71	35	22.3	7.4	-67	7.0	14.2	+103
Milan, Italy (Campo *et al.*)	72	12	20.8	6.2	-70	8.2	15.9	+93
	42	18	20.8	5.7	-67	8.2	14.1	+71
European Multicenter (Ramon *et al.*)	68	12	22.0	7.5	-66	8.4	11.6	+33
Sheffield, UK (Chapple *et al.*)	58	12	22.0	10.0	-54	8.8	11.6	+30
Ioannina, Greece (Giennekopoulos *et al.*)	50	12	22.4	9.1	-59	7.6	16.8	+121
Johannesburg, South Africa (Steele *et al.*)	41	12	22.4	7.0	-68	5.6	10.2	+54
	38	24	22.4	9.5	-57	6.6	11.0	+66
Australia (Millard *et al.*)	20	12	19.0	8.2	-56	3.0	11.4	+280
Summary‡ (world literature)	546	12	22.2	9.1	-58	7.8	13.8	+77
	176‡	24	21.8	8.5	-60	7.6	13.9	+82
	88	36	22.1	7.4	-66	7.5	14.5	+92

*For complete reference information, see Issa et al. [21].
†P = 0.01 to 0.0001.
‡First, second, and third rows summarize average improvement at first, second, and third years.

FIGURE 4-31. Following the first series of 12 transurethral needle ablation (TUNA) procedures performed in the United States in 1994, hundreds of patients have been treated worldwide under standardized protocols. The clinical results in terms of symptom score improvements and peak urinary flow rate improvements were reviewed by Issa *et al.* [21]. Overall, at 12 months, there was a decrease in symptom score from 22.2 to 9.1 (-60%), as well as a decrease at 3 years (-66%). Similarly, improvements in peak urinary flow rate from 7.8 to 13.8 mL/s at 1 year (+ 77%) were maintained at 2 years (+ 82%) and 3 years (+ 92%). (*Adapted from* Issa *et al.* [21].)

Detrusor Pressure Following Transurethral Needle Ablation of the Prostate

Study Group*	Patients, n	Follow-up, mo	Maximum Detrusor Pressure, cm H_2O			
			Baseline	Post-TUNA	Percent Change	P Value
US/Pilot Study (Issa *et al.*)	12	6	91.8	70.9	-22.7	0.094
Milan, Italy (Campo *et al.*)	12†	6†	74.5†	56.3†	-24.4	0.046
	108	3	85.3	53.2	-37.6	<0.01
	86	6	85.3	61.3	-28.1	<0.01
	72	12	85.3	63.7	-25.3	<0.01
	42	24	85.3	67.8	-20.5	<0.01
Johannesburg, South Africa (Steele *et al.*)	41	1	92.4	77.0	-16.6	<0.05
	39	3	92.4	68.5	-25.8	<0.05
	34	6	92.4	54.8	-40.6	<0.05
	29	12	92.4	72.9	-21.1	<0.05
	12	24	92.4	56.9	-36.2	<0.05
Sheffield, UK (Chapple *et al.*)	39	3	97.0	79.0	-18.5	>0.05
	39	12	97.0	84.0	-13.4	>0.05
Australia (Millard *et al.*)	20	6	70.7	59.9	-15.8	0.90

*For complete reference information, see Issa et al. [22].
†Indicates detrusor open pressure.

FIGURE 4-32. Detrusor pressures following transurethral needle ablation (TUNA) of the prostate. Five investigators performed invasive pressure-flow urodynamic studies before and at various times after therapy. The percent reduction in the maximum detrusor pressure ranged from -13.4% to -14.6%. All but one investigator found a statistically significant decrease in the maximum detrusor pressure. (*Adapted from* Issa *et al.* [22].)

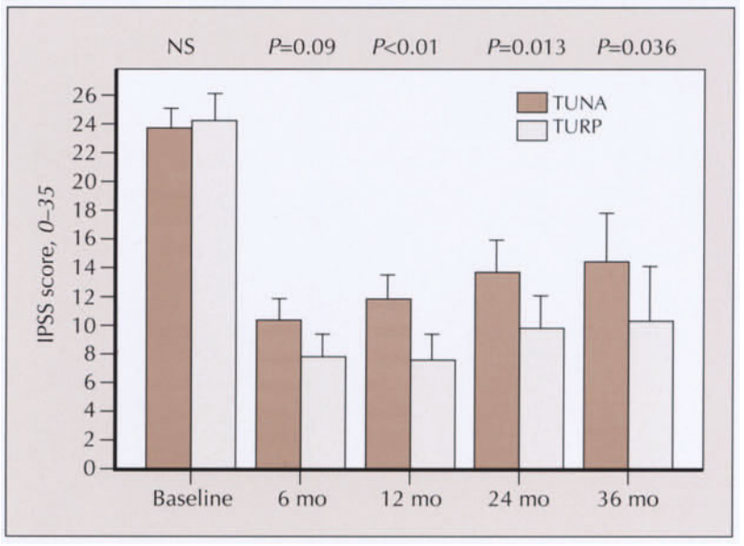


FIGURE 4-33. Transurethral needle ablation (TUNA) versus transurethral resection (TURP) American Urological Association (AUA) symptom score. In the United States, a multicenter, randomized trial was initiated in which patients were randomly assigned to either TUNA or a standard TURP procedure. Entry criteria included men with lower urinary tract symptoms and benign prostatic hyperplasia over the age of 45 years, with an AUA symptom score of 13 or greater, a peak flow rate of 12 mL/s or less, a prostate volume between 25 and 75 mL by transurethral ultrasound (TRUS), and a prostate-specific antigen level of less than 10 ng/mL. Sixty-five patients were randomly assigned to TUNA and 56 to TURP. Both groups were well matched in terms of demographics and baseline parameters prior to treatment. The mean age was 66.1 (65.8) years, and mean AUA symptom score was 23.9 (24.1). Prostate volume was 36.2 mL (35.7 mL by TRUS). Three-year data demonstrate a significant decrease in AUA symptom score from baseline at 6 months and all subsequent follow-ups. Although the initial decrease in AUA symptom score is almost identical between TUNA and TURP, a slight deterioration in symptom score is noted in the TUNA group for up to 2 years, after which no further change in symptom score occurs. IPSS—International Prostate Symptom Score; NS—not significant.

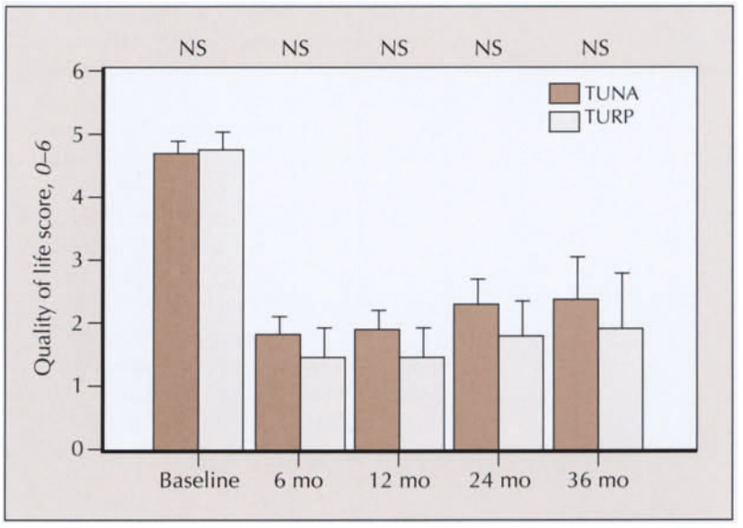


FIGURE 4-34. Quality of life score for transurethral needle ablation (TUNA) versus transurethral resection (TURP). Similar results are found for the quality of life score, which is equally improved in both TUNA and TURP groups with a slight deterioration in the TUNA group up to 2 years. (All differences from baseline in both groups are significant.) NS—not significant.

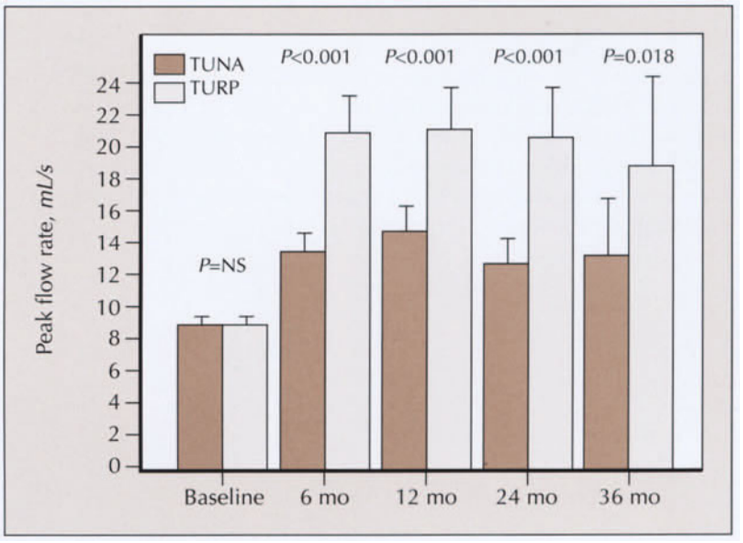


FIGURE 4-35. Transurethral needle ablation (TUNA) versus transurethral resection (TURP) peak flow rates. Although the TUNA-treated patients experience an improvement in peak urinary flow rate significantly different from baseline at all time points of follow-up, the TURP group achieved a statistically much larger improvement in flow rate that was maintained over the entire duration of follow-up.

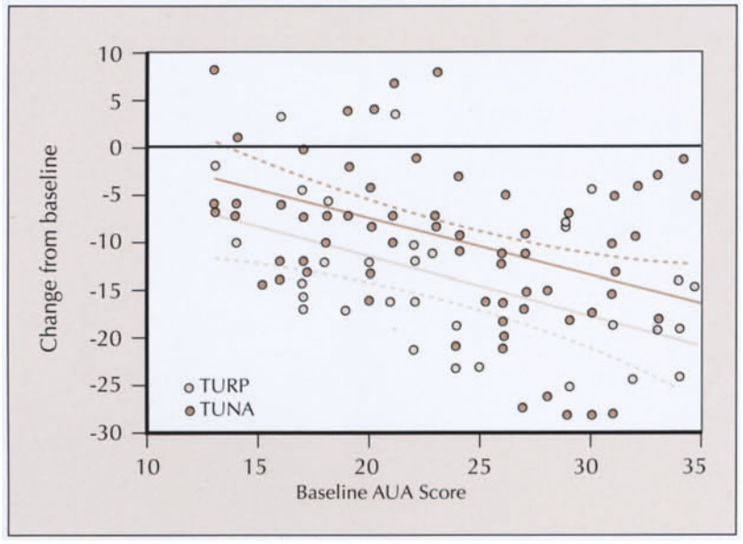


FIGURE 4-36. Transurethral needle ablation (TUNA) versus transurethral resection (TURP) baseline score versus change from baseline and linear regression. A convenient way to compare treatment efficacy in terms of symptom improvement is a plot depicting the baseline symptom severity score against the changes from baseline. It is evident that almost all patients with very few exceptions experienced a decrease from baseline (*ie*, below the 0 or no-change line). With more advanced symptom severity scores, more significant drops from baseline were observed. The regression lines for both TUNA- and TURP-treated patients indicate that across all symptom severity ranges, the TUNA-treated patients had almost the same symptomatic improvement as the TURP-treated patients. AUA—American Urological Association.

Baseline and 6-Month Data for TUNA and TURP

	TUNA		TURP		
Parameter	**Baseline**	**6 mo**	**Baseline**	**6 mo**	***P* Value†**
AUA SI	23.9	10.8	24.1	8.1	0.0288
	$P < 0.0001$*		$P < 0.0001$*		0.430
BII	7.1	2.3	8.1	1.8	0.170
	$P < 0.001$*		$P < 0.001$*		< 0.001
QOL	4.6	2.0	4.8	1.5	0.19
	$P < 0.001$*		$P < 0.0001$†		< 0.001
Q_{max}	8.8	13.5	75.8	54.9	
	$P < 0.0001$*		$P < 0.001$*		
P_{det} Q_{max} AG number	78.7 61.2	64.5 37.2	58.3	10.9	
	$P < 0.036$*		$P < 0.001$*		
	$P < 0.001$*				

*Comparison from baseline to 6 months within groups.
†Comparison at 6 months between groups.

FIGURE 4-37. Results of baseline and 6-month follow-up pressure-flow urodynamic studies performed in the US randomized trial. The transurethral needle ablation (TUNA)–treated patients achieved a decrease in detrusor pressure (P_{det}) at maximum urine flow (Q_{max}) from 78.7 to 64.5 cm H_2O ($P = 0.036$), whereas the transurethral resection (TURP)–treated patients achieved a decrease from 75.8 to 54.9 cm H_2O ($P < 0.01$). The Abrams-Griffith (AG) number, calculated as P_{det} at Q_{max} minus two times Q_{max}, decreased significantly in both treatment groups. AUA SI—American Urological Association Symptom Index; BII—BPH Impact Index; QOL—Quality of Life Question.

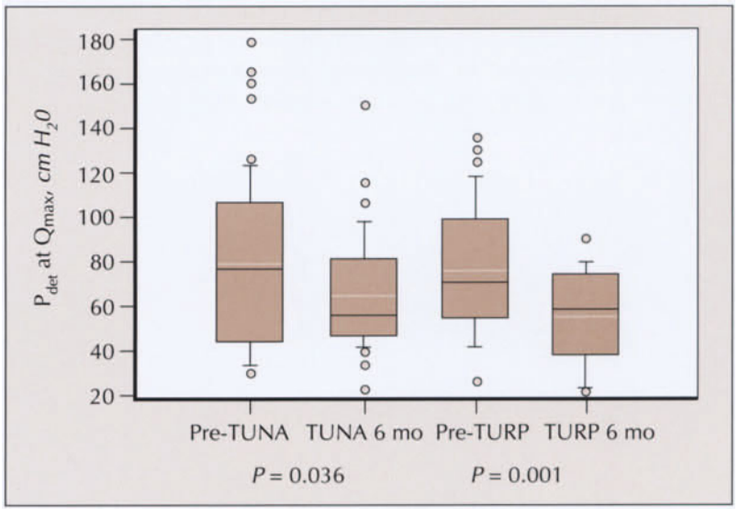
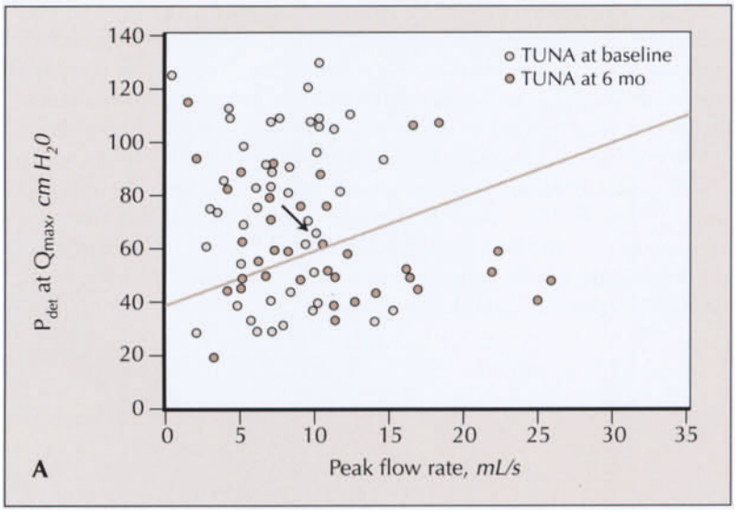


FIGURE 4-38. Baseline and 6-month data for transurethral needle ablation (TUNA) and transurethral resection (TURP). The detrusor pressure (P_{det}) at maximum urin flow (Q_{max}) for both TUNA- and TURP-treated patients before and 6 months after therapy demonstrate the overall decrease of the P_{det} at Q_{max} in both treatment groups. There was no statistically significant difference at 6 months between the two groups ($P = 0.19$).



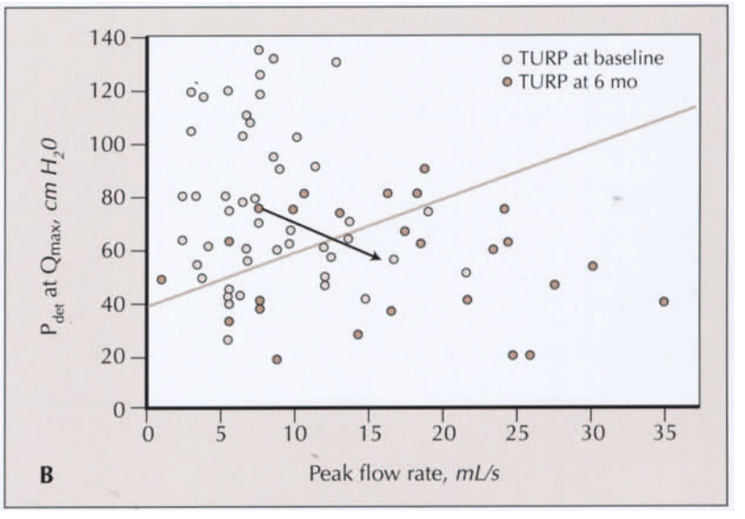


FIGURE 4-39. The detrusor pressure (P_{det}) maximum urine flow (Q_{max}) versus Q_{max} for transurethral needle ablation (TUNA) (**A**) or transurethral resection (TURP) (**B**) treated patients at baseline and 6 months. When plotting P_{det} at Q_{max} versus Q_{max} in the traditional form of an Abrams-Griffith nomogram, it is apparent that overall the TURP-treated patients move from the obstructed to the equivocal and nonobstructed category (*arrow*), whereas the overall change in the TUNA-treated patients is less pronounced, and more patients remain in the obstructed category [23]. *Straight line* indicates equivocal.

TUNA Versus TURP Adverse Events

	TUNA, n (%)	*TURP, n (%)*
Bleeding	21 (32.3)	56 (100)
Retrograde ejaculation	0 (0)	21 (38.2)
Urinary tract infection	5 (7.7)	7 (12.7)
Urethral stricture	1 (1.5)	4 (7.3)
Erectile dysfunction	0 (0)	7 (12.7)
Incontinence	0 (0)	2 (3.6)
Dysuria	0 (0)	2 (3.6)

FIGURE 4-40. Transurethral needle ablation (TUNA) versus transurethral resection (TURP) adverse events. The TUNA procedure is remarkably free of adverse events. No cases of retrograde ejaculation, erectile dysfunction, or urinary incontinence were seen, and the most common adverse event noted was hematuria. Urinary retention has been reported between 13.3% and 41.6% [25]. The retention is transient and lasts usually less than 72 hours. Anesthetic requirements for the TUNA procedure vary from patient to patient and from physician to physician. Some investigators perform the TUNA procedure in an office setting with intraurethral lidocaine or intravenous solution only; others prefer an operating room setting with either monitored intravenous sedation or other forms of general anesthesia.

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5

Laser Prostatectomy

John N. Kabalin

Laser prostatectomy can remove obstructing benign prostatic hyperplasia (BPH) tissue without the hospitalization, bleeding, and perioperative and postoperative morbidity caused by transurethral resection of the prostate (TURP). Laser wavelengths suitable for urologic applications can be delivered through small semiflexible fibers that pass through standard endoscopes. The tissue effects of laser energy usually involve virtually instantaneous attainment of temperatures above 60°C to create coagulation or above 100°C to create vaporization. Laser energy can be delivered using a free-beam delivery system to create coagulation necrosis, vaporization, or tissue cutting. In addition, a diffusing laser fiber can be placed directly into the adenoma for interstitial treatment, to create coagulation necrosis.

Laser prostatectomy has undergone an amazingly rapid evolution since its introduction in the late 1980s. The free-beam coagulation technique is not commonly used and has been replaced by the holmium resection technique when an immediate effect of TURP is desired, and by interstitial techniques when a delay in clinical improvement can be tolerated. Laser techniques in the prostate continue to evolve as urologists pursue the goal of removing the obstructing adenoma with minimal side effects and maximum clinical improvement.

Lasers in Common Clinical Use for Prostatectomy

Laser	*Wavelength, nm*	*Physical Characteristics and Tissue Interaction*
Holmium:YAG	2140	Rapid tissue absorption and heating **Tissue vaporization and incision** Tissue coagulation effects at lower energy densities
Neodymium:YAG Semiconductor diode KTP	1064 800–1000 532	Slower, more diffuse tissue absorption and heating **Tissue coagulation** Tissue vaporization effects at very high energy densities

FIGURE 5-1. Common laser wavelengths used for various prostatic surgical applications. KTP—potassium-titanyl-phosphate; YAG—yttrium-aluminum-garnet.

TRANSURETHRAL ULTRASOUND-GUIDED LASER-INDUCED PROSTATECTOMY

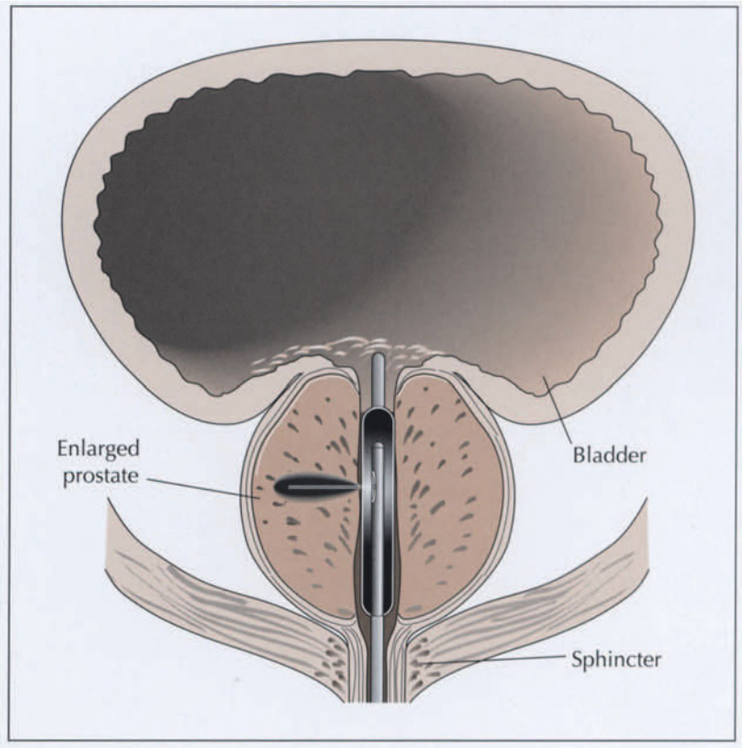
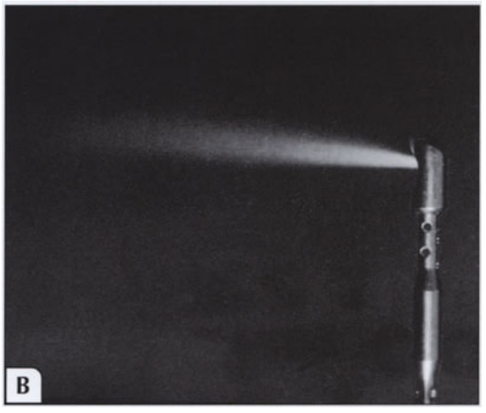
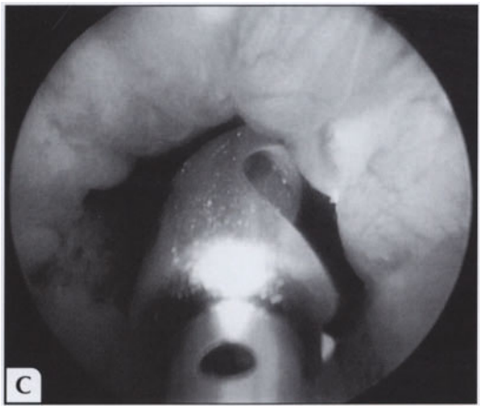
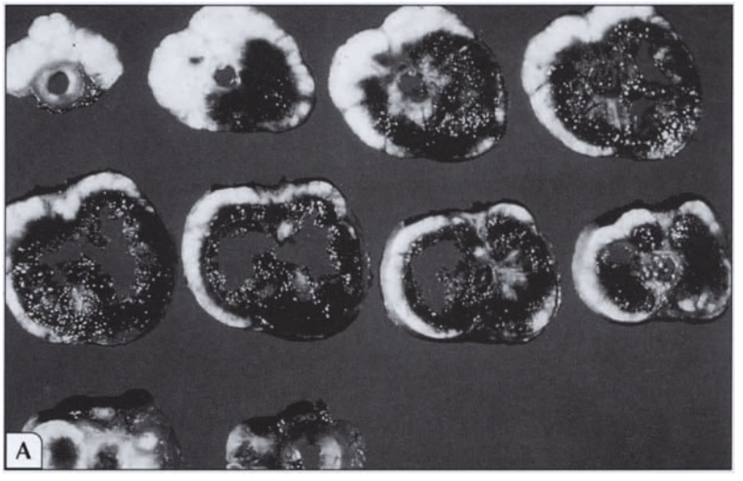


FIGURE 5-2. The first delivery system designed specifically for free-beam laser prostatectomy was developed in the late 1980s [1]. The transurethral ultrasound-guided laser-induced prostatectomy (TULIP [Intrasonix Inc., Burlington, MA]) device was a uniquely engineered apparatus consisting of a 22-F rigid urethral probe containing an Nd:YAG (neodymium:yttrium-aluminum-garnet) delivery fiber with a deflecting prism mechanism. It was the first system developed to deflect laser energy laterally into the prostatic lateral lobes to produce coagulation necrosis. Clinical results demonstrated efficacy [2], although less than that of transurethral resection of the prostate. The device and ultrasound imaging proved cumbersome, and the procedure disappeared. However, the efforts of the TULIP investigators inspired much of the subsequent development of free-beam laser prostatectomy.

FIGURE 5-3. The Nd:YAG wavelength is well suited for transmission through flexible fibers, which are easily manipulated through standard urologic endoscopes and applied under direct vision [3]. This allows for visually guided prostatic irradiation. **A,** Distal reflecting mirror of the side-firing Nd:YAG laser delivery fiber for prostatic irradiation (Urolase; CR Bard and Trimedyne, Covington, GA). **B,** This fiber allows the laser beam to be aimed directly at the lateral or median lobe of the prostate under direct vision. **C,** Visual cystoscopic appearance of the laser fiber in use. The fiber is directed at obstructing tissue and held in place during the irradiation.







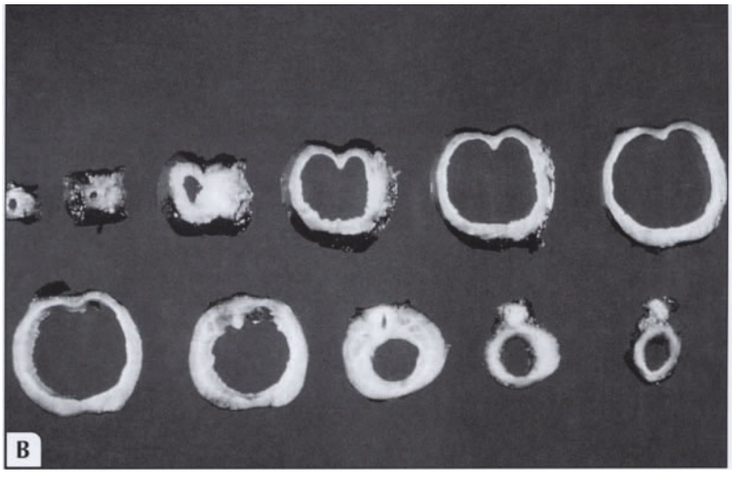
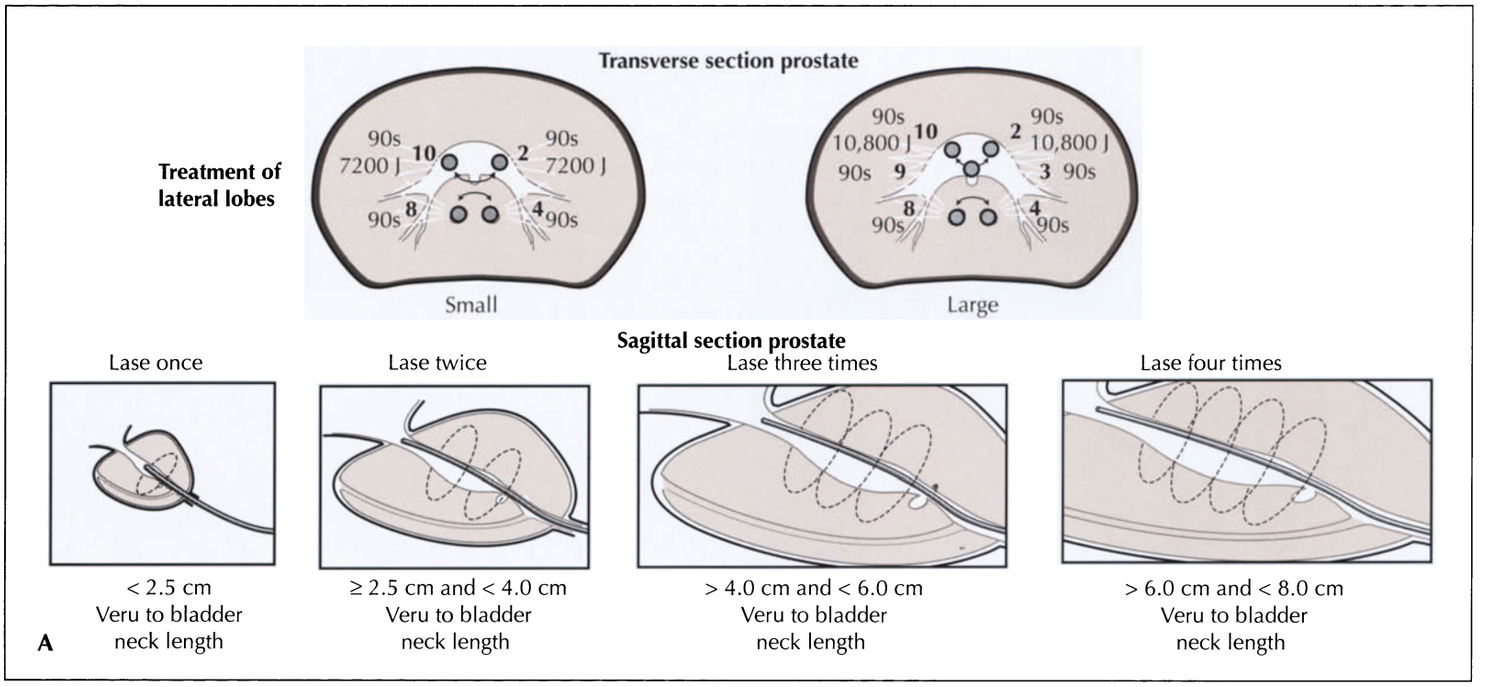


FIGURE 5-4. Tissue coagulation. Because the Nd:YAG wavelength is relatively poorly absorbed by water, energy transfer to tissue is slow when it is used at lower energy density applications. Thus, tissue coagulation is favored over tissue vaporization. In canine feasibility studies, Johnson *et al.* [4] demonstrated that the Nd:YAG laser created a large volume of coagulation necrosis, and that resolution of this lesion resulted in enlargement of the prostatic fossa. This pioneering work led to clinical investigations of safety and efficacy in humans with benign prostatic hyperplasia. **A,** Serial transverse section of the canine prostate immediately after Nd:YAG irradiation demonstrating the area of coagulation necrosis (*dark tissue*). **B,** The cavity formed 7 weeks later. (*From* Johnson *et al.* [4]; with permission.)



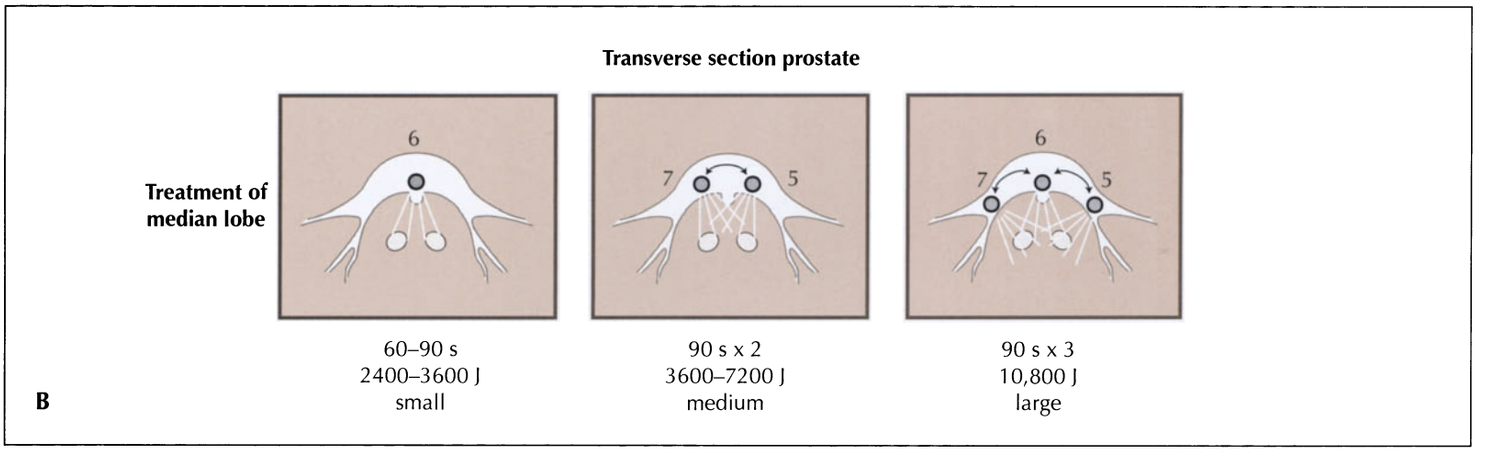


FIGURE 5-5. Prostatectomy using the Nd:YAG laser typically is performed under regional or general anesthesia. A cystoscope of relatively small caliber (≤ 22 F) accommodates almost all side-firing laser fibers used for Nd:YAG laser prostatectomy. Because Nd:YAG laser coagulation seals blood vessels, preventing both bleeding and intraoperative fluid absorption (and, thus, transurethral resection syndrome), sterile water or saline irrigation commonly is used. Room temperature irrigation dissipates the heat more effectively, and thus is preferred over warm irrigation. In the spot-coagulation technique described by Kabalin [5], the Nd:YAG laser fiber is held in close approximation, without touching the obstructing benign prostatic hyperplasia tissue. Laser energy is applied for a minimum of 60 to 90 seconds, and power settings between 40 and 60 W are used, depending on the degree of divergence of the emitting laser fiber. If the laser is applied without causing tissue char, the depth of coagulation necrosis is approximately 1.5 cm. Areas of coagulation necrosis eventually undergo dissolution and pass in the urinary stream over several weeks.

A, All obstructing lateral lobe benign prostatic hyperplasia (BPH) tissue is sequentially irradiated with multiple spot laser energy applications. A typical treatment consists of spot laser energy application at 2- and 4-o'clock positions (left lateral lobe) and 8- and 10-o'clock positions (right lateral lobe) in the transverse plane. For larger prostates with greater anteroposterior dimensions, further spot laser applications may be needed no more than 1.5 cm apart to ensure treatment of all tissue. For larger, longer prostates, spot laser energy applications are repeated in sequential transverse planes every 1.5 cm along the length of the gland from bladder neck to the veru montanum, until all obstructing lateral lobe BPH is irradiated.

B, The median lobe is similarly treated with spot laser energy applications. For larger median lobes, multiple spot laser treatments across the breadth of the median lobe (no more than 1.5 cm apart) are performed until all obstructing median lobe BPH is irradiated.

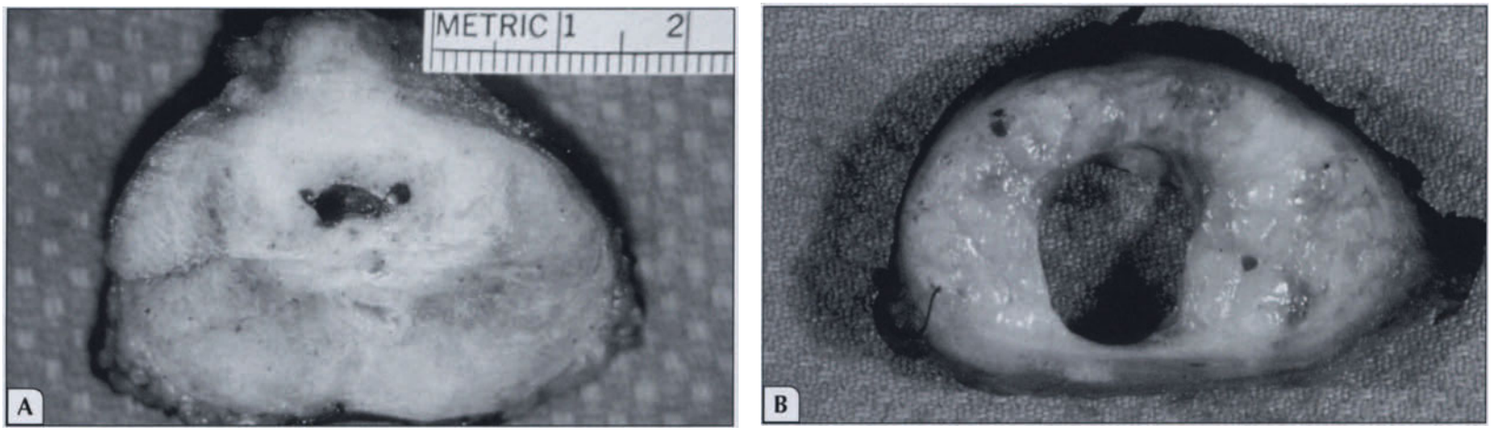


FIGURE 5-6. The acute and chronic tissue effects of Nd:YAG laser spot applications have been demonstrated in vivo by Kabalin *et al.* [6]. **A,** A transverse section through a human prostate removed immediately after Nd:YAG laser spot applications. The transition zone shows extensive coagulation necrosis. **B,** A transverse section through a human prostate removed 1 year after Nd:YAG laser spot applications. The transition zone slough is complete, leaving a large laser defect.

A. Complications of Nd:YAG Laser Prostatectomy in 230 Men With 1-year Minimum Postoperative Follow-up

	Incidence, n (%)
Acute complications	
Significant hemorrhage/transfusion	0 (0)
Transurethral resection syndrome	0 (0)
Prostatic perforation/extravasation	0 (0)
Postoperative prostatitis	6 (2.6)
Long-term complications	
Stress urinary incontinence	0 (0)
Urethral stricture	4 (1.7)
Bladder neck contracture	10 (4.3)
Reoperation for residual tissue	13 (5.7)

B. Voiding Outcomes of Nd:YAG Laser Prostatectomy From 20 Combined Series Reporting 3 to 12 Months' Postoperative Follow-up

		Postoperative (n)		
	Preoperative (n)	*3 mo*	*6 mo*	*12 mo*
Peak flow rate, *mL/s*	8.0 (1765)	16.2 (1306)	16.2 (1433)	17.2 (600)
Postvoid residual, *mL*	189 (1295)	63 (1104)	61 (1044)	72 (576)
AUA symptom index	21.3 (1851)	8.4 (1308)	7.4 (1466)	7.0 (618)

C. Long-term Voiding Outcomes of Nd:YAG Laser Prostatectomy

		Postoperative (n)		
	Preoperative (n)	*1 y*	*2 y*	*3 y*
Peak flow rate, *mL/s*	7.7 (290)	16.9 (193)	17.1 (84)	19.7 (18)
Postvoid residual, *mL*	334 (273)	120 (175)	117 (84)	111 (17)
AUA symptom index	19.9 (289)	7.8 (218)	8.8 (101)	5.7 (20)

FIGURE 5-7. Outcomes. After Nd:YAG free-beam laser prostatectomy, most patients are sent home with an indwelling catheter in place for several days. After the catheter is removed, voiding gradually improves over the next 6 to 12 weeks, as coagulation necrosis and dissolution of obstructing benign prostatic hyperplasia tissue occur. **A,** In a detailed analysis of complications associated with Nd:YAG free-beam laser prostatectomy in 230 men observed over a minimum 12-month follow-up and median 35-month follow-up, acute morbidity was relatively rare and limited in severity, whereas long-term complications compared very favorably with those associated with transurethral resection of the prostate.

B, Numerous published reports document the efficacy of Nd:YAG free-beam laser prostatectomy in improving all voiding parameters.

C, Observed voiding improvement has been durable through at least 3 years of treatment with this technique [7–10]. AUA—American Urological Association.

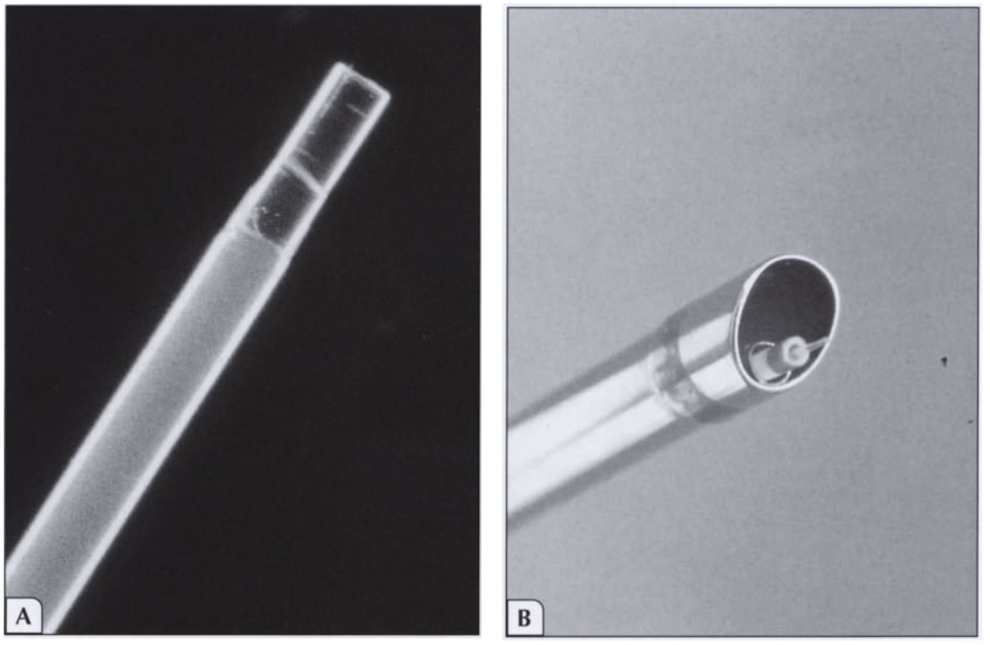


FIGURE 5-8. Tools used for Ho:YAG laser resection of the prostate (HoLRP). The Ho:YAG wavelength is highly absorbed in tissue water, producing rapid heating with tissue vaporization and incision. Initial clinical trials by Kabalin [11] showed that transurethral Ho:YAG vaporization of the prostate was safe but also demonstrated the inefficiency of trying to vaporize large volumes of benign prostatic hyperplasia (BPH) tissue with existing fiber delivery systems. This led to development of a much more practical and efficient technique for HoLRP by Kabalin [12] in the United States and Gilling *et al.* [13] in New Zealand, who showed that this technique provides much more rapid and more consistent clinical outcomes than Nd:YAG laser prostatectomy [14].

True prostatic resection can be performed with the Ho:YAG laser, with immediate transurethral vaporization and excision of all obstructing BPH tissue elements. Thermal effects of the Ho:YAG laser seal tissue planes during incision much better than does electrocautery, providing excellent hemostasis and minimal intraoperative fluid absorption during transurethral resection. Acute complications are thus minimized compared with transurethral resection of the prostate [15]. HoLRP is routinely performed with just overnight catheterization postoperatively and can be performed on an outpatient basis.

A, HoLRP is most commonly performed with a bare, end-firing, flexible laser fiber, although side-firing fibers are also available for this laser wavelength. The pulsed Ho:YAG laser is used at high power settings, typically 80 to 100 W, to maximize efficiency in tissue vaporization and incision. **B,** A continuous flow rectoscope that incorporates a fixed channel to minimize movement and vibration at the distal end of the laser fiber is used. Normal saline solution is used for irrigation.

A. Steps in Holmium Laser Resection of the Median Lobe

1–2: Incise posterior bladder neck deeply at 5- and 7-o'clock positions, extending these incisions along the prostatic urethra to the veru montanum
3–4: Connect these incisions in front of the veru montanum
5: Work retrograde, back toward the bladder neck, undermining and excising the median lobe
6: Consider dividing a larger median lobe into smaller pieces to facilitate tissue removal

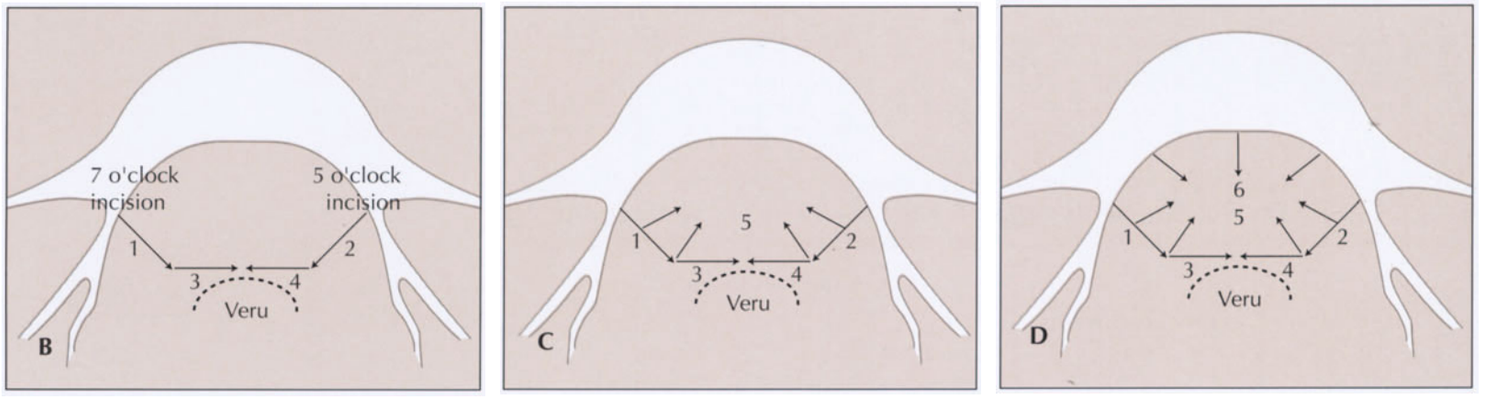
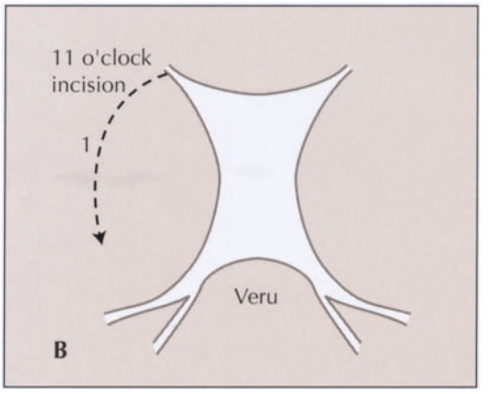
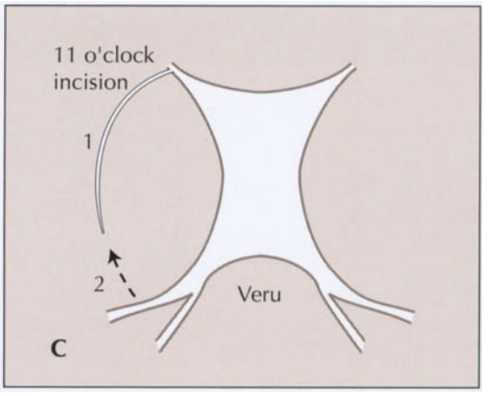


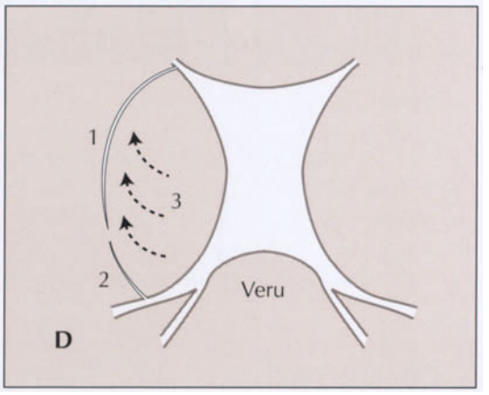
FIGURE 5-9. Ho:YAG laser resection of the prostate (HoLRP): median lobe. **A,** HoLRP begins with resection of the median lobe of the prostate in sequential steps (1–6). **B,** Posterior bladder neck incisions are made at the 5- and 7-o'clock positions on either side of the median lobe and carried down to the level of the veru montanum. These are then joined in the midline in front of the veru montanum. **C,** The median lobe is next undermined in a retrograde fashion, working back toward the bladder neck. **D,** The median lobe is excised. Before excision of the median lobe, the surgeon should consider cutting it into smaller pieces to facilitate evacuation from the bladder.

A. Steps in Holmium Laser Resection of the Lateral Lobes

1: On right, make deep template incision to surgical capsule anteriorly at 11-o'clock position, extending this from bladder neck to the level of the veru montanum
2: Incise upward from the floor of the prostatic fossa along the length of the lateral lobe from bladder neck to the level of the veru montanum
3: Connect these incisions at the apex of the lateral lobe at the veru montanum, and then work retrograde back toward the bladder neck, undermining and excising the lateral lobe. Again, consider dividing a larger lobe into smaller pieces to facilitate tissue removal
4–6: Repeat steps to resect the left lateral lobe, beginning with a deep template incision to surgical capsule anteriorly at the 1-o'clock position







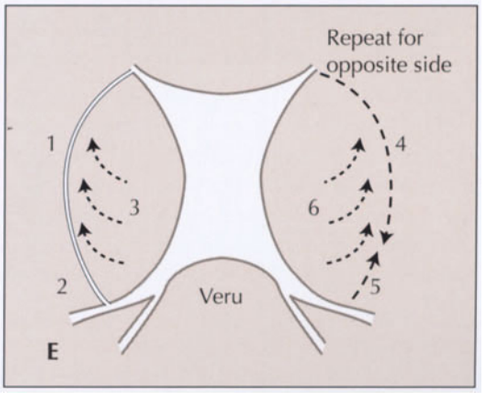
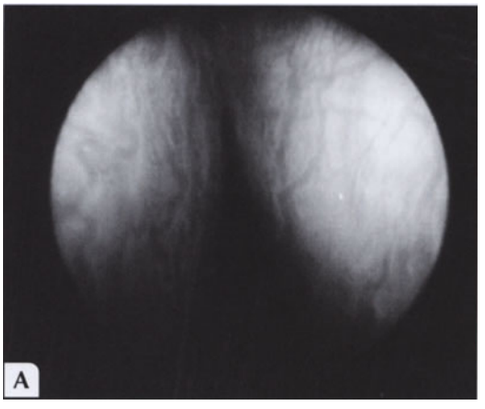


FIGURE 5-10. Ho:YAG laser resection of the prostate (HoLRP): lateral lobes. **A,** HoLRP proceeds with resection of the lateral lobes of the prostate, again in sequential steps. **B,** Beginning with the right lateral lobe, an anterior template incision is made at the 11-o'clock position and carried laterally to the surgical capsule of the prostate, then extended along the length of the lateral lobe from the bladder neck to the level of the veru montanum. **C,** A second incision is made upward from the floor of the prostate and also extended along the length of the lateral lobe from bladder neck to veru montanum. **D,** These incisions are connected at the apex of the lateral lobe at the veru montanum, and the resection continues along the previously identified plane of the surgical capsule in a retrograde fashion back toward the bladder neck, undermining and excising the lateral lobe. **E,** Before complete excision of the lateral lobe, the surgeon should consider cutting it into smaller pieces to facilitate tissue evacuation from the bladder. These steps are then repeated in sequence for resection of the left lateral lobe of the prostate.



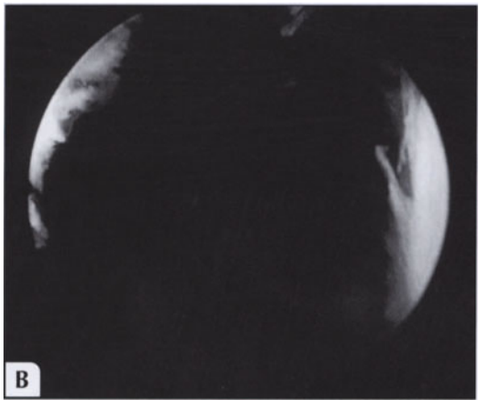
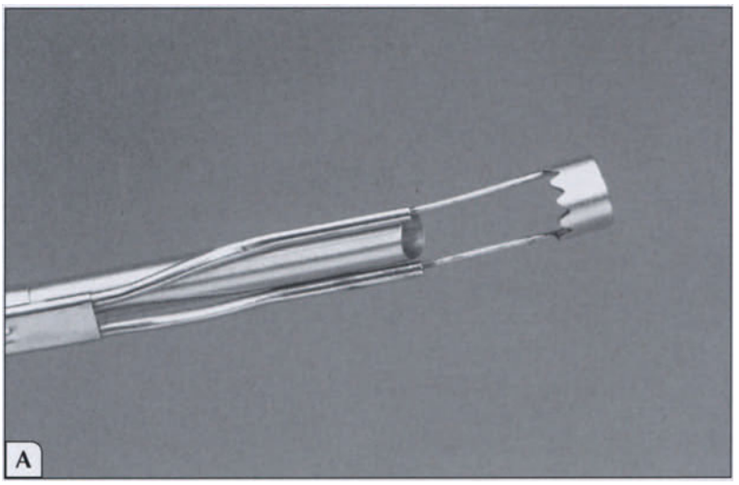


FIGURE 5-11. Complete hemostatic removal of all obstructing benign prostatic hyperplasia tissue with Ho:YAG resection of the prostate (HoLRP). **A,** Obstructing prostate viewed endoscopically before resection. **B,** Wide-open unobstructed prostatic fossa viewed immediately after HoLRP. Complete and immediate tissue removal mimics transurethral resection of the prostate or open enucleation prostatectomy, with far superior hemostasis and much lower associated morbidity.



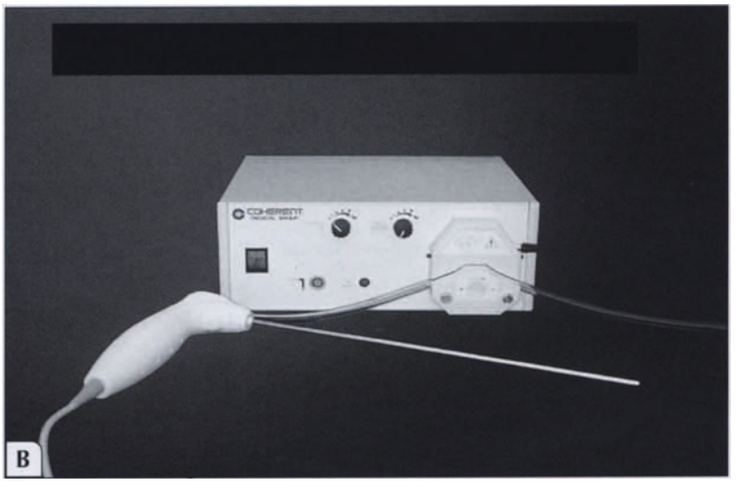


FIGURE 5-12. Tools for excising prostate tissue segments. During Ho:YAG laser resection of the prostate, larger or smaller prostate tissue segments can be excised at the discretion of the surgeon. **A,** For larger pieces of tissue, a heavy, reinforced grasping loop has been designed to fit a standard resectoscope working element and may be used to grab and extract tissue from the bladder. **B,** Alternatively, in a more efficient approach to Ho:YAG laser resection of the prostate that is particularly applicable to very large glands, entire lobes of the prostate can be undermined and enucleated whole into the bladder [16,17]. A specially designed transurethral tissue morcellation device (VersaCut; Coherent Medical Group, Santa Clara, CA) is then used to mince and evacuate this tissue from the bladder. This procedure can be called "Ho:YAG laser enucleation of the prostate" (HoLEP) and is anatomically similar to classic open surgical enucleation of the prostate.

A. Complications of Ho:YAG Laser Resection of the Prostate in 61 Men With 1-Year Postoperative Follow-up

	Incidence, n (%)
Acute complications	
Significant hemorrhage/transfusion	0 (0)
Transurethral resection syndrome	0 (0)
Prostatic perforation/extravasation	0 (0)
Urinary tract infection	3 (4.9)
Long-term complications	
Stress urinary incontinence	1 (1.6)
Urethral stricture	6 (9.8)
Bladder neck contracture	1 (1.6)
Reoperation for residual tissue	0 (0)

B. Voiding Outcomes of Ho:YAG Laser Resection of the Prostate From Eight Combined Series Reporting 3 to 12 Months' Postoperative Follow-up (*n*=619)

	Preoperative	*Postoperative*	*Change, %*
Peak flow rate, *mL/s*	8.5	21.2	+149
AUA symptom index	21.0	5.5	- 74

FIGURE 5-13. Outcomes. **A,** Complications and overall morbidity associated with Ho:YAG laser resection of the prostate (HoLRP) are minimal. In a randomized prospective direct comparison of HoLRP with standard electrosurgical transurethral resection of the prostate (TURP), Gilling *et al.* [15] observed significantly fewer complications associated with HoLRP. **B,** Voiding outcomes for HoLRP demonstrate efficacy equal to standard TURP for relief of bladder outlet obstruction [18]. AUA—American Urological Association.

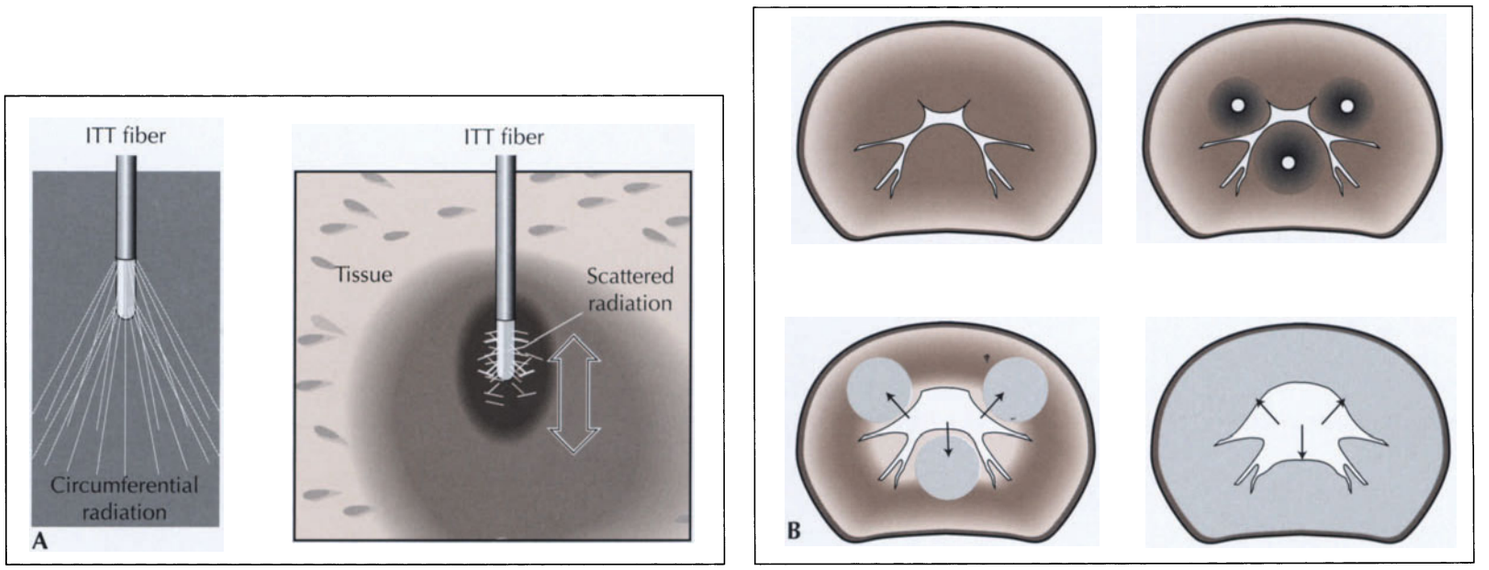


FIGURE 5-14. Interstitial laser coagulation (ILC) of the prostate. ILC is performed using specialized laser delivery fibers that are inserted transurethrally directly into the obstructing benign prostatic hyperplasia (BPH) tissue. These interstitial thermal therapy (ITT) fibers are designed to emit diffuse laser radiation circumferentially along the distal segment of the fiber. Nd:YAG or semiconductor diode lasers are typically used to perform ILC. In contrast to free-beam laser prostatectomy approaches described previously, ILC selectively targets BPH tissue deep to the prostatic urethral surface, attempting to spare the urethral mucosa. **A,** Using a diffusing ITT laser fiber buried within the BPH adenoma, a timed laser application is performed with radiation of laser energy and resulting thermal effects, creating a zone of coagulation necrosis within the prostate. **B,** Multiple interstitial laser applications are repeated, depending on the size of the prostate, encompassing obstructive medial lob and lateral lobe tissue. During the next several weeks, the resulting zones of coagulation necrosis undergo involution with gradual reduction in prostate volume to relieve bladder outlet obstruction.

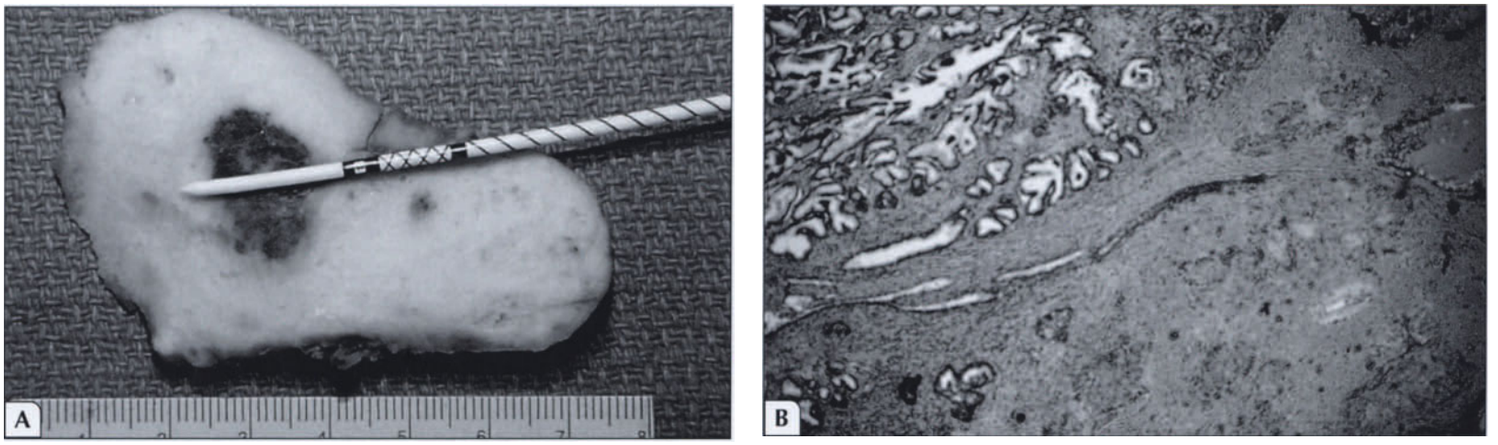


FIGURE 5-15. Regions of coagulation necrosis in a prostatectomy specimen. **A,** An open prostatectomy specimen removed 5 days after interstitial laser coagulation with the laser fiber positioned to recreate treatment conditions. The *dark area* represents coagulation and hemorrhagic necrosis. The coagulation zone correlates with the predicted region of treatment based on the diffusing delivery fiber. **B,** A photomicrograph demonstrating the necrosis grossly identified in **A**. The lower half demonstrates necrosis. Note the sharp demarcation between the treated zone and the untreated benign prostatic hyperplasia tissue. Indigo interstitial laser fiber shown in **A**. (Indigo Medical, Cincinnati, OH).

A. Complications of Interstitial Laser Coagulation of the Prostate in 239 Men With 1-Year Postoperative Follow-up

	Incidence, n(%)
Acute complications	
Significant hemorrhage/transfusion	1 (0.4)
Transurethral resection syndrome	0 (0)
Prostatic perforation/extravasation	0 (0)
Urinary tract infection/epididymitis	6 (2.5)
Long-term complications	
Stress urinary incontinence	1 (0.4)
Urethral stricture	9 (3.8)
Bladder neck contracture	4 (1.7)
Reoperation for residual tissue	23 (9.6)

B. Voiding Outcomes of Interstitial Laser Coagulation of the Prostate

		Postoperative		
	Preoperative (n = 239)	***3 mo (n = 239)***	***6 mo (n = 216)***	***12 mo (n = 198)***
Peak flow rate, *mL/s*	7.7	16.3	17.9	17.8
Postvoid residual, *mL*	151	32	18	19
AUA symptom index	25.4	8.1	6.1	6.1

FIGURE 5-16. Interstitial laser coagulation (ILC) of the prostate is typically performed as an outpatient procedure. Postoperatively, patients experience significant prostatic edema and require catheter drainage of the bladder for at least several days after treatment. **A,** Although acute complications associated with ILC therapy are uncommon, the long-term reoperation rate for residual benign prostatic hyperplasia tissue is relatively high compared with other operative techniques. **B,** ILC is capable of producing good voiding outcomes with a minimally invasive approach. AUA—American Urological Association. (*Data from* Muschter and Hofstetter [19].)

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Transurethral Resection and Incision of the Prostate, and Open Prostatectomy for Benign Prostatic Hyperplasia

6

Rolf Muschter

Together with open prostatectomy, the most common surgical procedures for benign prostatic hyperplasia (BPH) are transurethral (electro-) resection of the prostate (TURP) and transurethral incision of the prostate (TUIP). Their common root is lithotomy, which was done since the 16th century with instruments inserted into the urethra. Development of the early resectoscope depended on many scientific advances, such as the cystoscope, the incandescent lamp, and the vacuum tube, which made possible the development of an electrosurgical unit for coagulation and cutting of tissue. Modern transurethral resection and incision is based on improved materials and engineering, fiberoptic light sources, rod lens systems, video cameras, and high-tech electrosurgery generators. Open prostatectomy also improved with the developments of modern surgery such as anesthesia, blood transfusion, and antibiotics. To date, common techniques are using the perineal, retropubic, and suprapubic transvesical approach.

Certain complications of benign prostatic hyperplasia are considered a definite requirement for surgical intervention. These complications are acute refractory urinary retention, recurrent urinary tract infection, recurrent hematuria, bladder stones, and renal insufficiency secondary to obstructing benign prostatic hyperplasia (BPH).

Although TURP continues to be the operation most commonly done for benign disease of the prostate and the reference standard for treatments used in the management of BPH-related lower urinary tract symptoms, the number of TURPs performed declined by 52% between 1989 and 1995 (Holtgrewe, AUA Health Policy Brief). This decline represents the impact of newer medical treatments as well as the availability of less invasive surgical treatments. The morbidity and mortality of TURP is quite low, but still exists. However, TURP achieves excellent clinical results with a low retreatment rate.

The TUIP procedure is best done in smaller glands with a minimal amount of lateral lobe tissue and a high posterior lip of the bladder, forming what has been called a primary bladder contracture configuration. In such cases it is a safe and effective method, with its main advantages being reduced operative time, bleeding, and incidence of retrograde ejaculation.

Open prostatectomy certainly removes more completely all adenomatous tissue and achieves the best clinical results with the lowest retreatment rate; however, it is highly interventional and has a considerable morbidity and mortality. Conversely, TURP in patients with very large glands (*ie*, ≥ 100 g) can be associated with significant fluid absorption, intraoperative bleeding, and intraoperative and immediate postoperative complications. Therefore, the open procedure usually is reserved for patients with larger glands (*ie*, > 80 g). The decision whether to do a TURP or open prostatectomy depends on the urologist's training and surgical skills in resecting larger glands.

POSITIONING FOR SURGERY

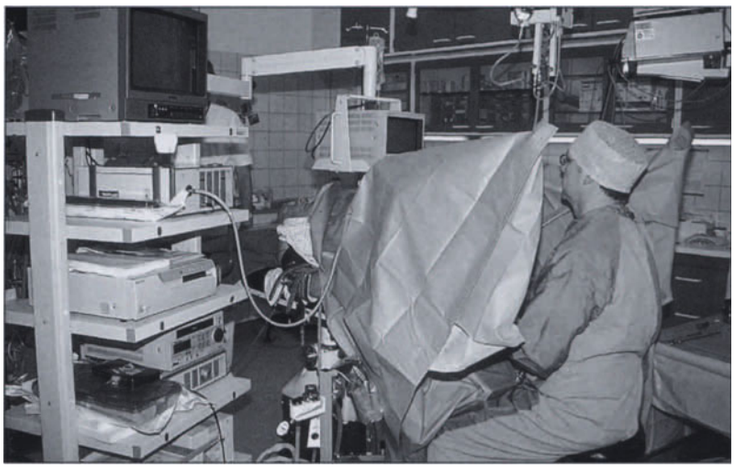


FIGURE 6-1. Patient positioning and operating room equipment for performing transurethral resection and incision of the prostate. The patient is on the operating table in a lithotomy position.

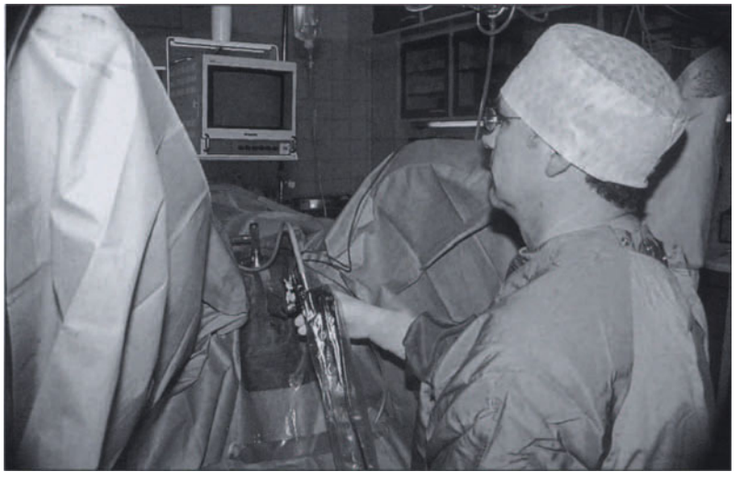


FIGURE 6-2. Position of the surgeon performing a video-assisted transurethral resection of the prostate.

TRANSURETHRAL RESECTION OF THE PROSTATE

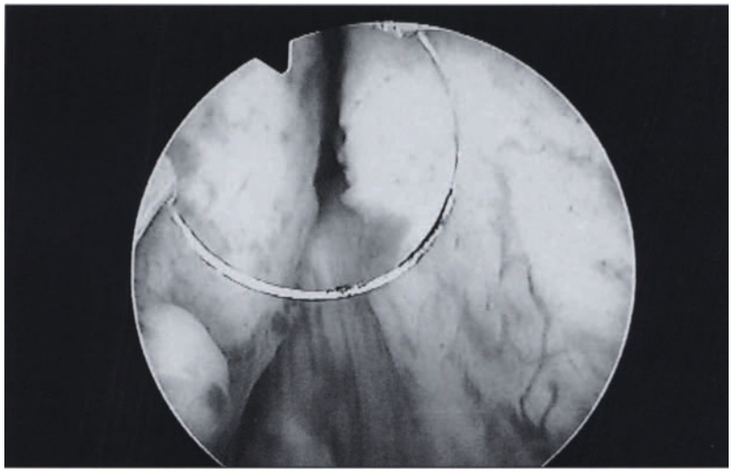


FIGURE 6-3. Endoscopic view of benign prostatic hyperplasia. This view before resection shows the relationship of the prostate lobes to the bladder and verumontanum and the size of the loop.

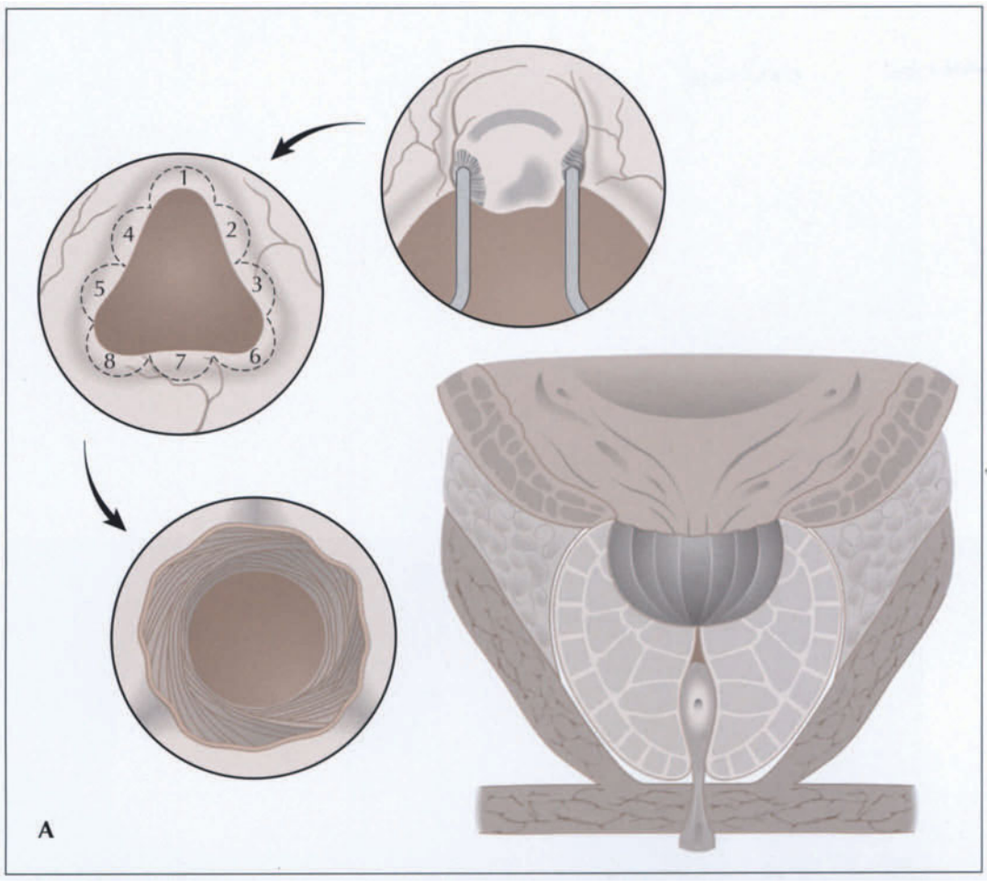
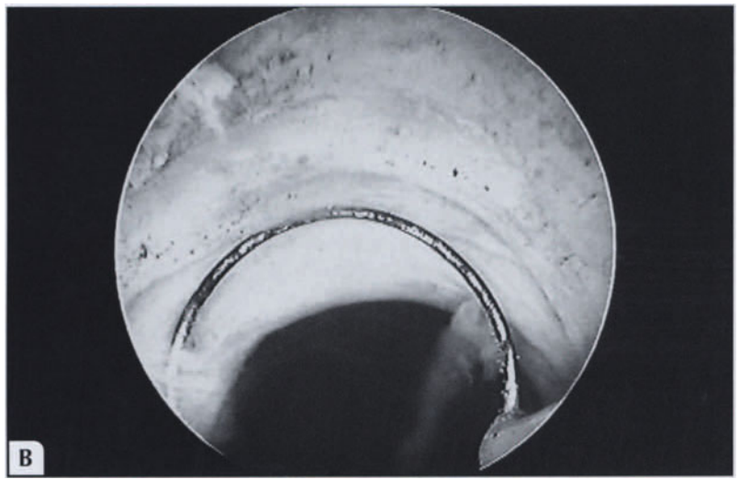
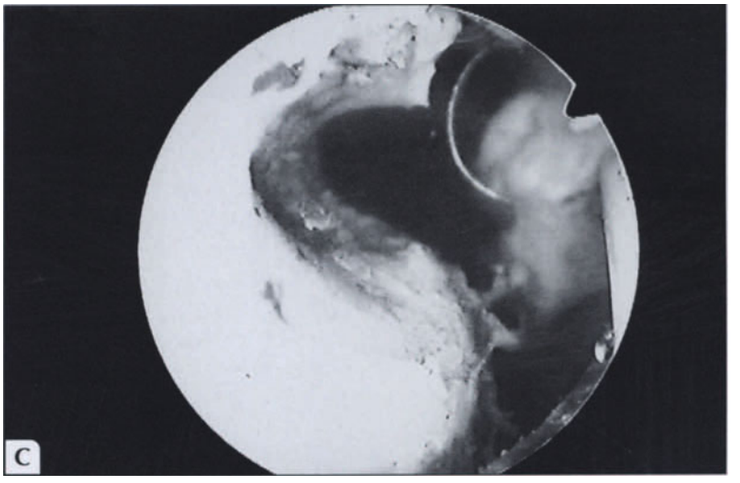
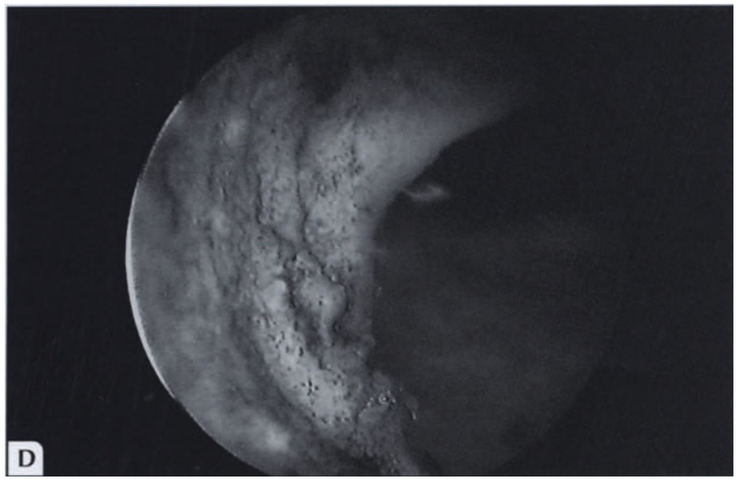
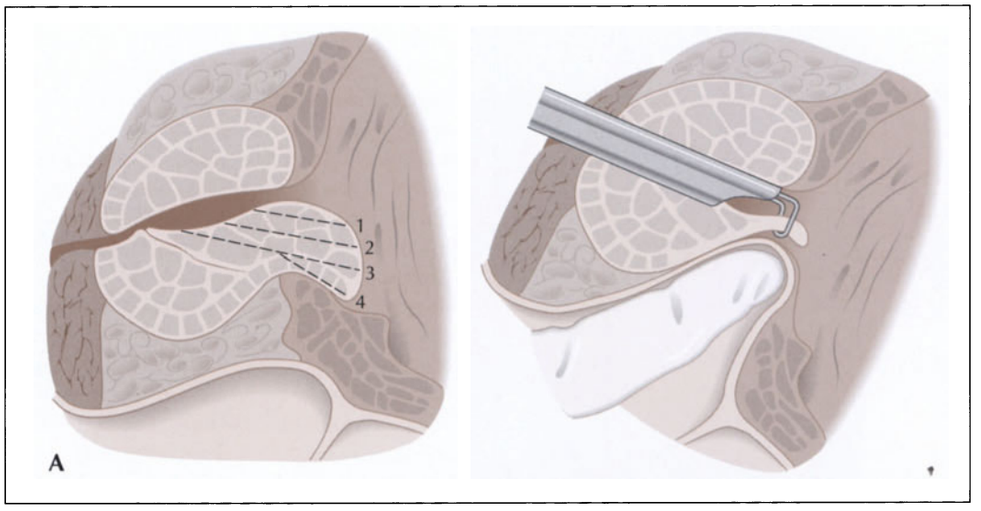


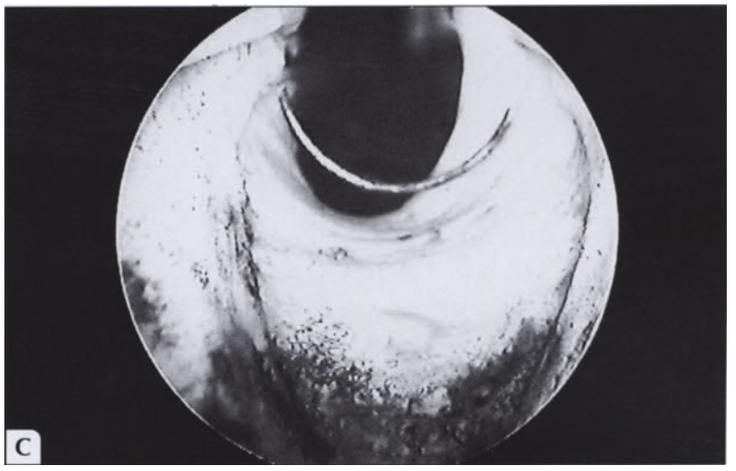
FIGURE 6-4. Transurethral resection of the prostate (TURP): stage 1. **A,** Schematic representation of stage 1. There are a number of ways of resecting the prostate, but all should be done in a step-by-step, orderly fashion to control the bleeding so that a precise anatomic dissection of the adenoma can be done. The Nesbit three-staged technique is illustrated here. The bladder is distended with approximately 100 mL of fluid to demarcate more clearly the prostate, the bladder neck, and the bladder wall. An initial cut is made anteriorly at 12 o'clock with the resectoscope loop. The incision is carried deeply until the seemingly circular fibers of the bladder neck are exposed. The resection is carried to approximately the 3 o'clock position, and bleeding points are carefully controlled. The resection is then continued counterclockwise from 12 to 9 o'clock, in a similar fashion. The resection is completed from the 3 to 9 o'clock position. **B,** Deep anterior cut at 12 o'clock. **C,** First incision of the anterior part of the right side lobe. **D,** Incompletely resected prostatic fossa at the end of stage 1 of TURP.











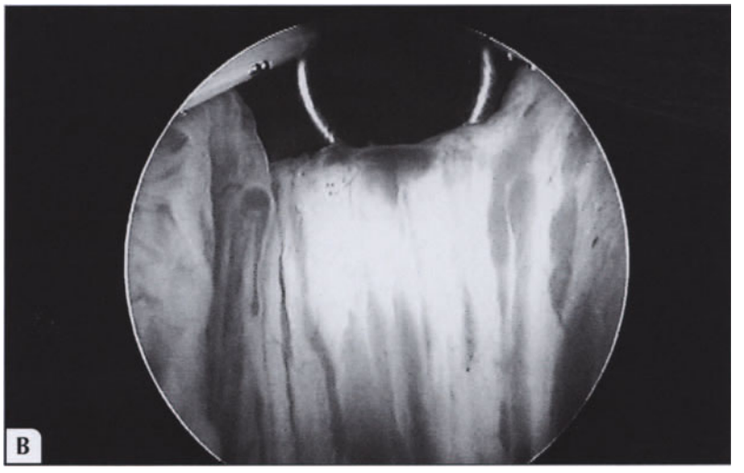
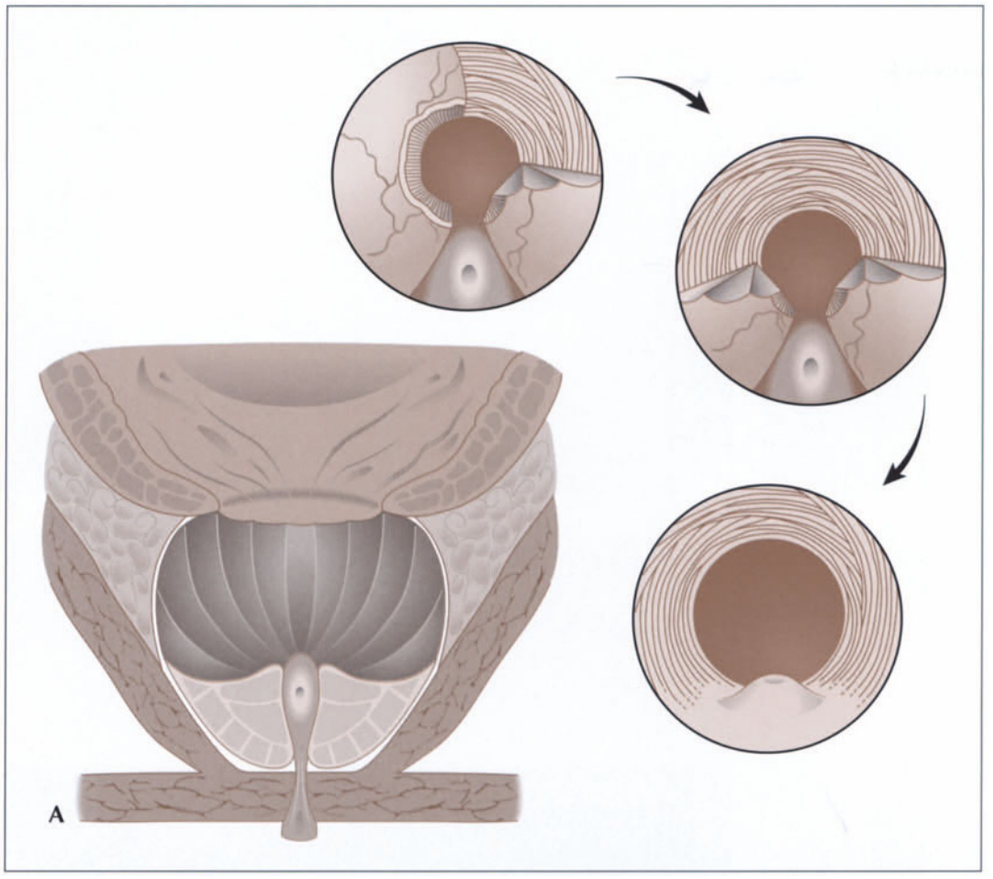
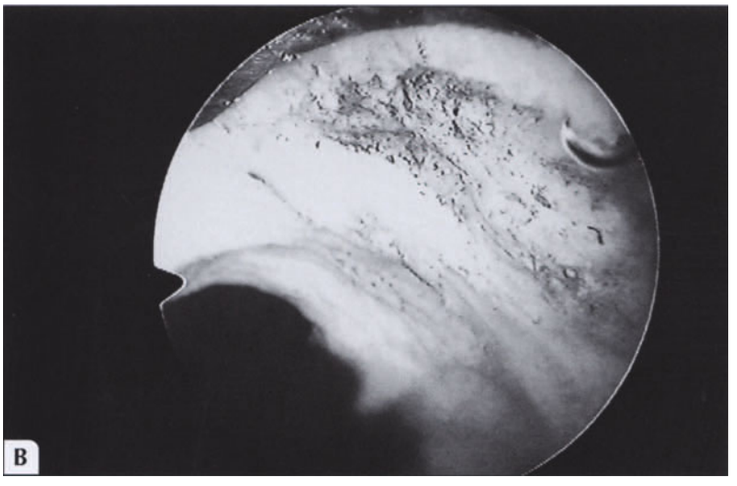


FIGURE 6-5. Resecting the median lobe. **A,** Schematic representation. The median lobe is resected by going back and forth from left to right then right to left and resecting it level by level (1 to 4, *left*). At this point, manipulation of the prostate floor and median lobe with the finger in an O'Connor rectal sheath (*right*) facilitates the resection. If the anatomy of the gland is that of a primary vesical neck contracture, or what has been called a "median bar," one or two incisions at 6 o'clock or at 5 and 7 o'clock are made through the bladder neck at the end of the procedure if the neck is very prominent. **B,** Endoscopic view of the median bar before transurethral resection. **C,** Resection of the median lobe in the 6 o'clock position down to the capsule.





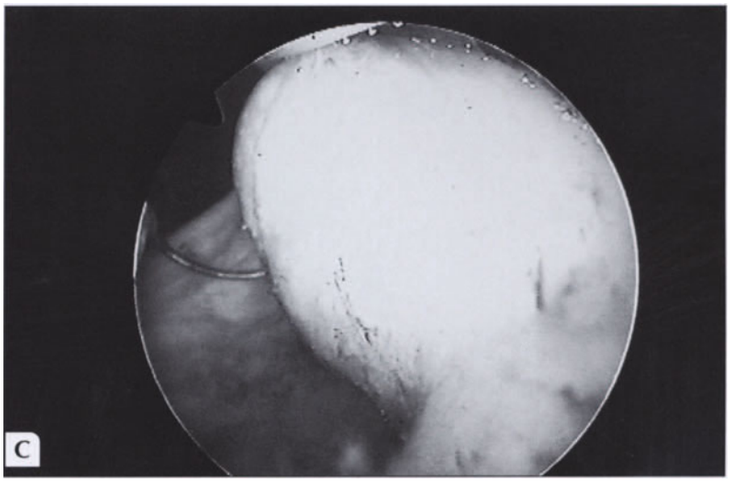


FIGURE 6-6. Transurethral resection of the prostate: stage 2. **A,** Schematic representation. Depending on the length of the prostatic fossa, the resectoscope is placed in front of the verumontanum and the resection is begun at the 12 o'clock position. Resection is done again by quadrants, first from 12 to 3 o'clock, with bleeding points controlled as necessary. Resection is carried down until the surgical capsule of the prostate is identified. The quadrant from 12 to 9 o'clock is resected. When resecting the two posterior quadrants, the resection is usually taken down from the 9 o'clock to the 7 o'clock position, resecting most of the bulk of the lateral lobe. It is moved to the other posterior quadrant, which is resected similarly from 3 to 5 o'clock. The floor is resected last, if required, manipulating the tissue with the finger in the O'Connor sheath. Fibers readily identified on the roof and sides of the prostate usually are not as apparent on the floor. **B,** Resection at the 12 o'clock position. **C,** Beginning of the resection of the posterior quadrant of the left lobe.

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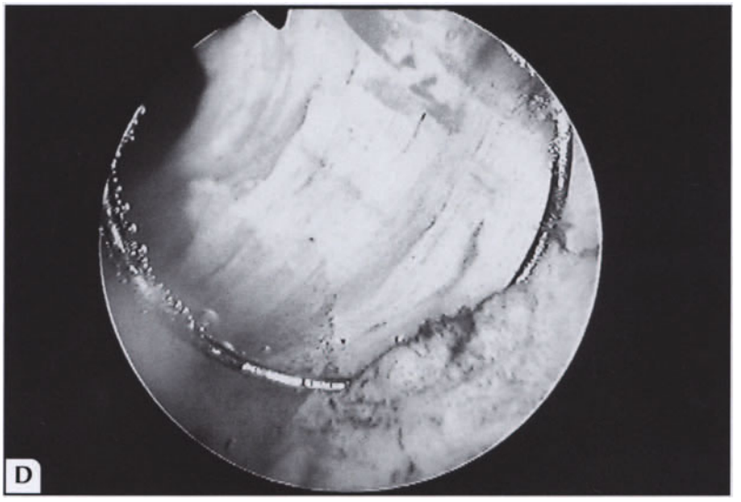


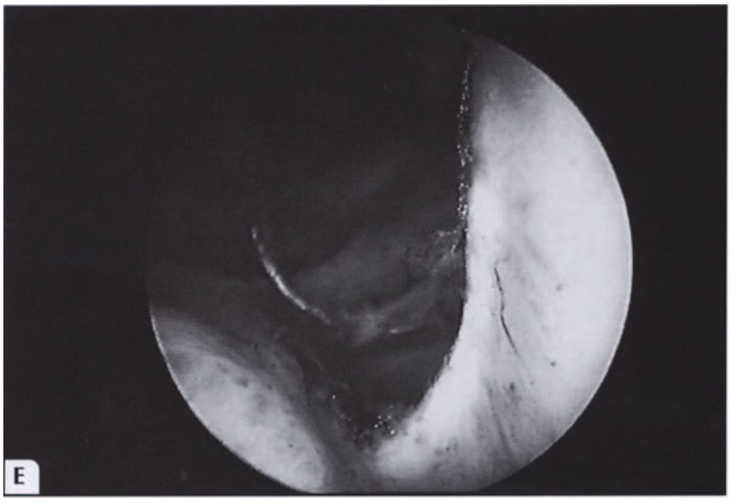
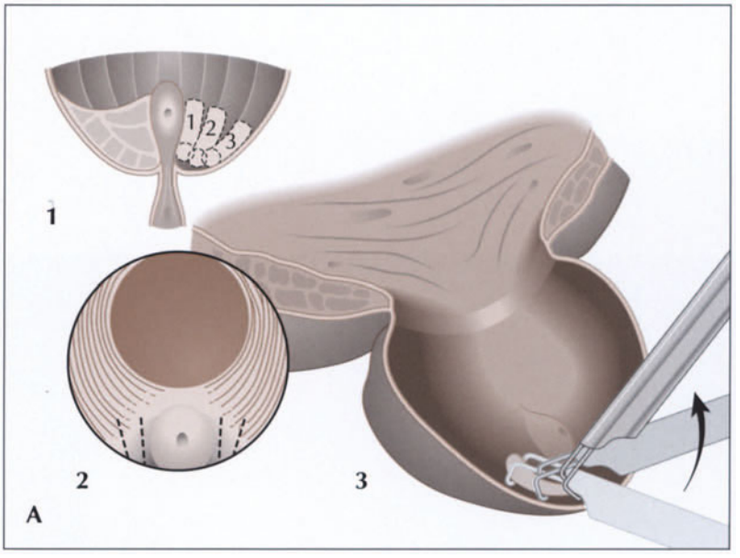


FIGURE 6-6. *(Continued)* **D,** Resection of the posterior quadrant of the left lobe until the surgical capsule is identified. **E,** View of the prostatic fossa at the end of stage 2. Apical tissue is not completely resected.



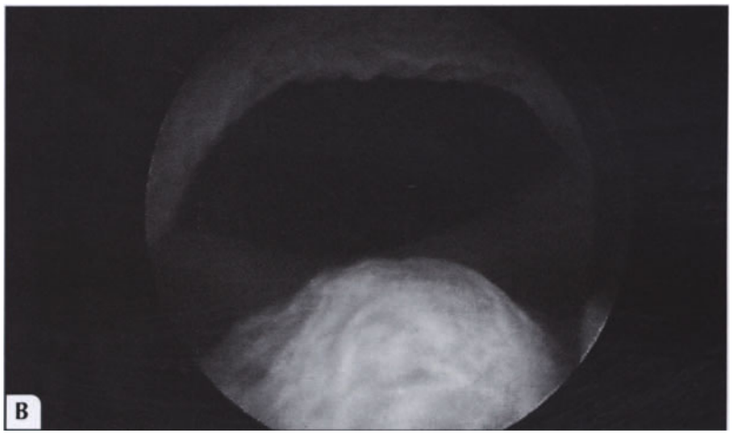


FIGURE 6-7. Transurethral resection of the prostate: stage 3. **A,** Schematic representation. The external sphincter and the verumontanum are identified. The tissue lying next to the verumontanum at the 5 and 7 o'clock positions is removed carefully with the resectoscope. The resection now is begun at the apex, proceeding from 7 to 12 o'clock. Use of a lateral-to-medial sweep of the resectoscope loop in response to the concavity of the gland can be helpful as adenomatous tissue is removed. Care must be taken not to advance the scope inward or, more significantly, not to retract the scope out during the resection, thereby inadvertently injuring the external sphincter. The resection is then carried out similarly from 5 to 12 o'clock. Bleeding is carefully controlled. In a larger gland, the lateral lobe tissue of the apex may project beyond the verumontanum into the sphincter area. In such cases, it is advisable to leave a thin rim of apical prostatic tissue rather than risk inadvertently resecting the sphincter.

B, Endoscopic view of the verumontanum, the sphincter, and the empty prostatic fossa at the end of stage 3 of the transurethral resection.

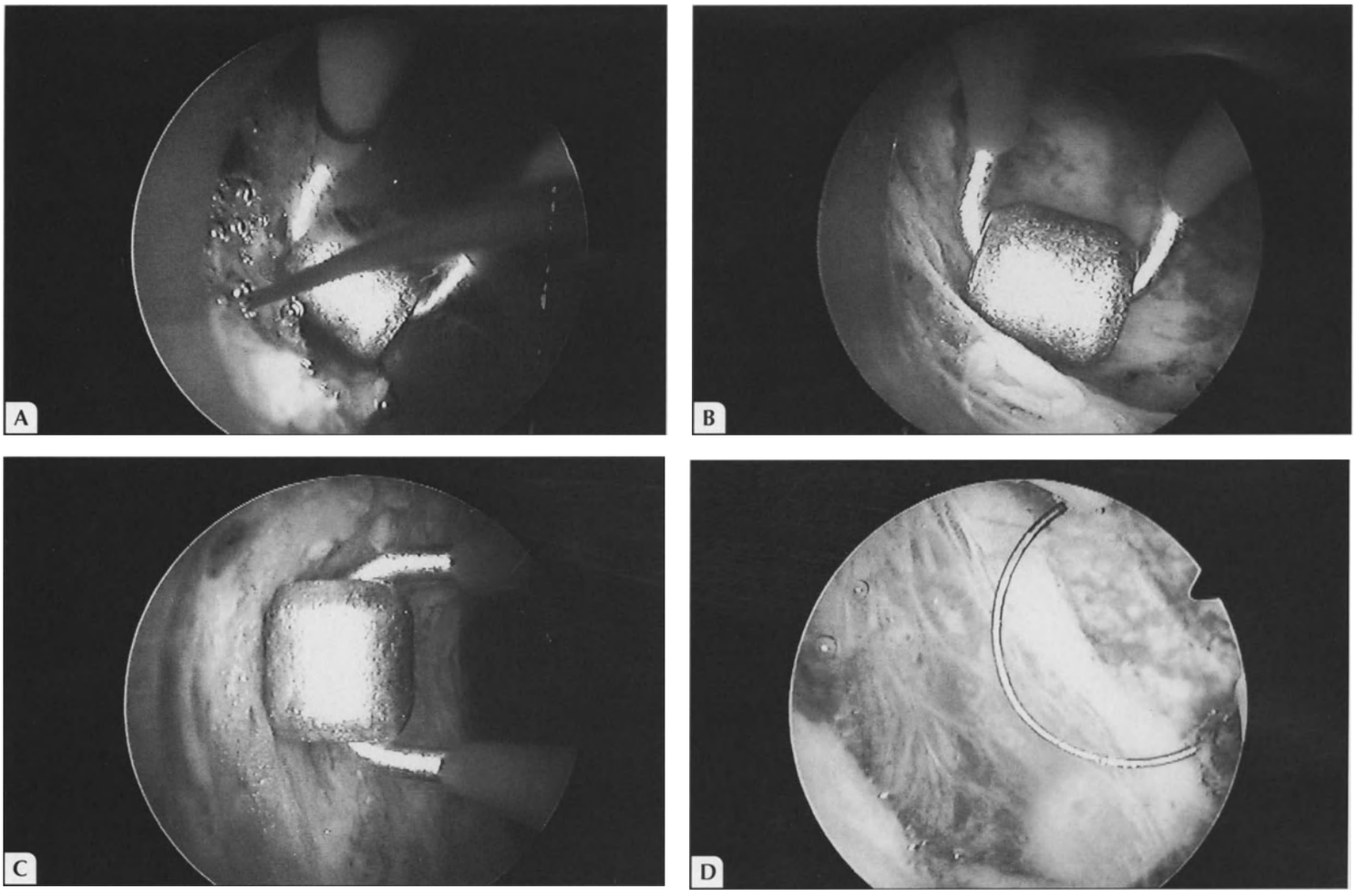


FIGURE 6-8. Transurethral prostatectomy continued. **A,** Surgical landmarks for transurethral prostatectomy. Note the arterial bleeding point. Control of bleeding is done by coagulation, *eg*, using a ball-shaped electrode.

B, Venous sinus exposed. Venous bleeding appears cloudlike when the water flow is reduced. **C,** Globules of fat protruding. **D,** Perforation of the surgical capsule. If there has been extensive resection of the prostatic capsule, it will be necessary to terminate the operation because of excessive absorption of fluid into the periprostatic tissue and venous complexes.

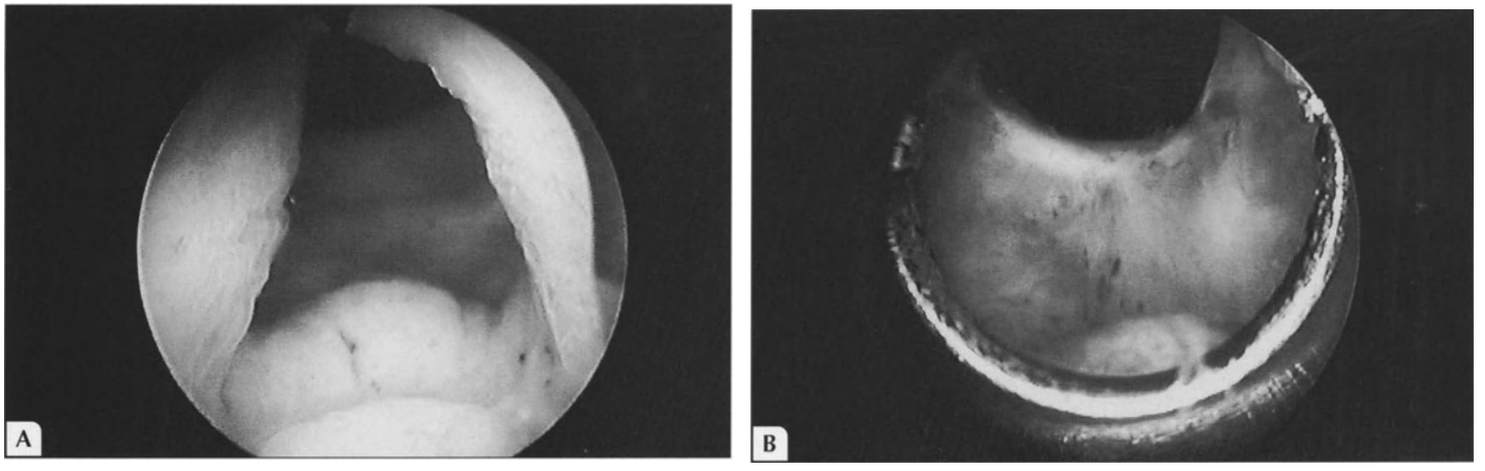


FIGURE 6-9. Complications of transurethral prostatectomy. **A,** Insufficient clinical outcome (incomplete apical resection). **B,** Bladder neck stricture.

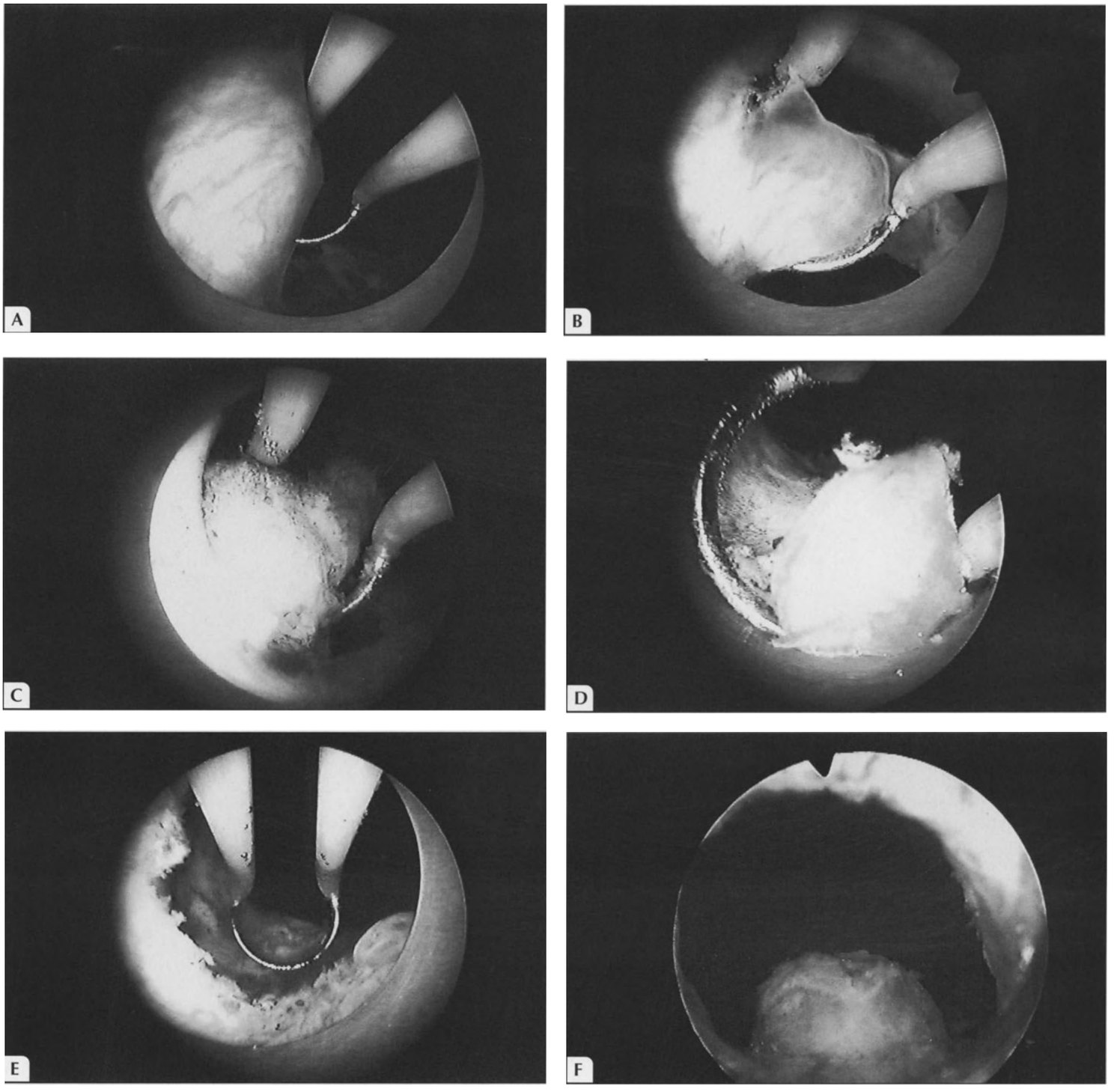
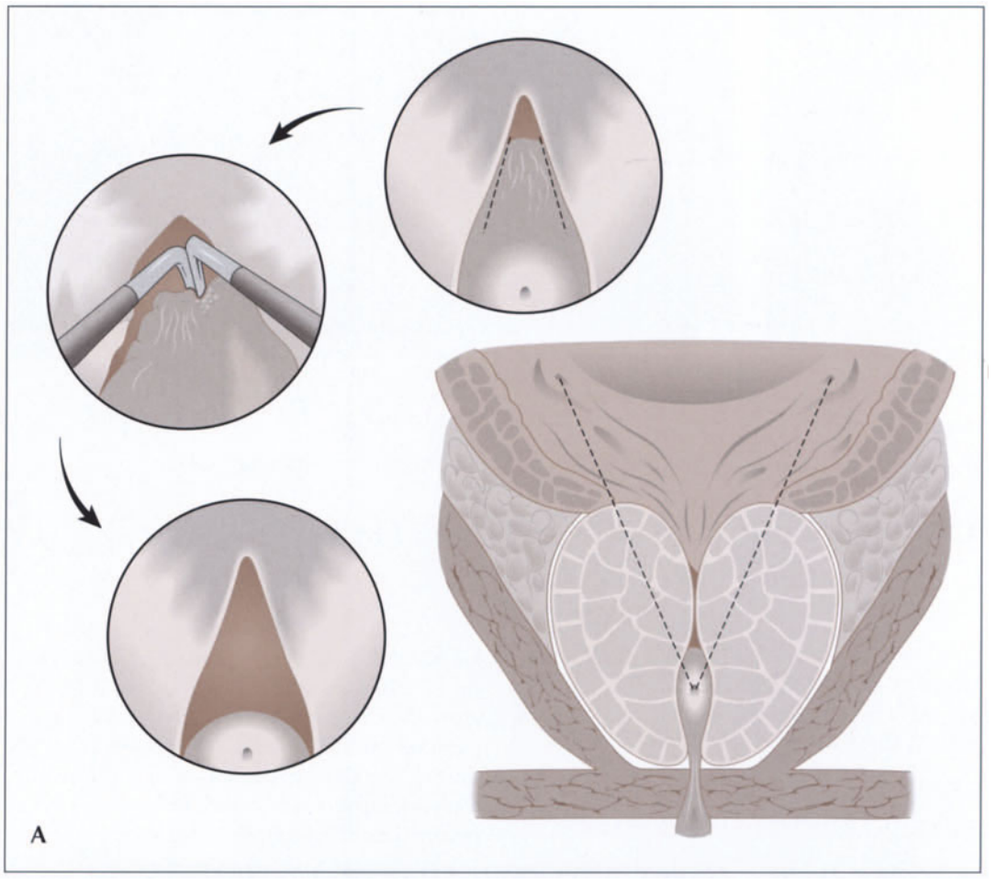
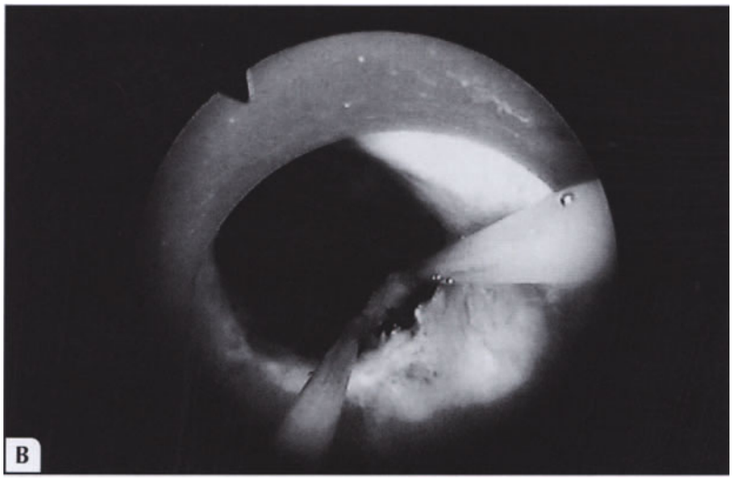


FIGURE 6-10. Modified transurethral resection of the prostate using a "thick loop" for better hemostasis. The increased mass of the loop slows down cutting speed but improves coagulation. During resection, some of the tissue water is vaporized. A to D, Resection of the apex right side lobe. E, Resection of prostate almost completed. F, This endoscopic view shows the verumontanum, the sphincter, and the empty prostatic fossa at the end of resection.





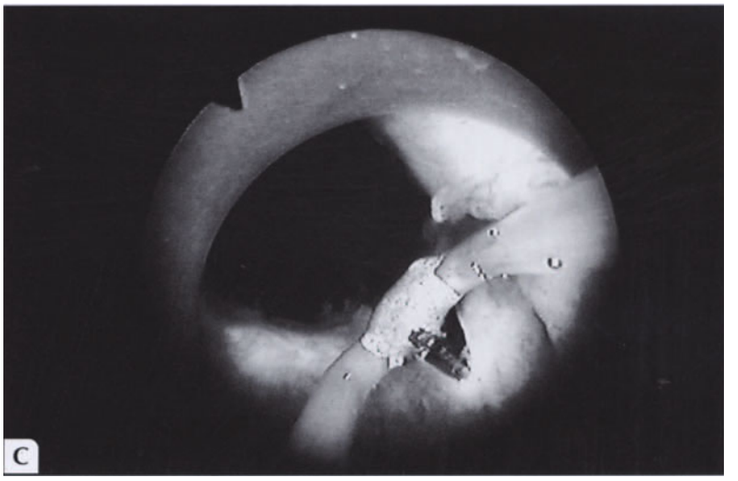


FIGURE 6-11. Transurethral incision of the prostate (TUIP): schematic representation. **A,** TUIP is started at the right ureteral orifice and continued through the bladder neck. The depth through the bladder neck should expose the shiny, filmy fibers at the vesical-prostate junction. The incision is then carried through the floor of the prostate down to the capsule. A corresponding incision is carried out similarly from the left ureteral orifice to the verumontanum. Bleeding is carefully controlled. **B** to **D,** Endoscopic view of transurethral incision of the prostate in the 5 o'clock position.

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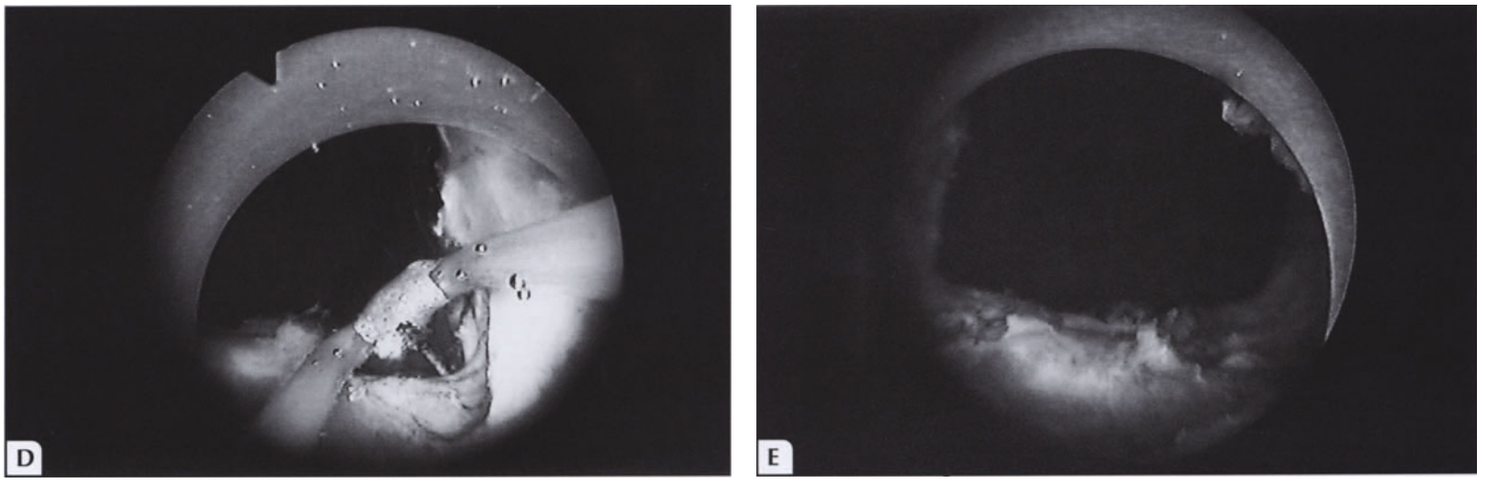

FIGURE 6-11. ***(Continued)*** Cuts are consecutive. **E,** Endoscopic view of the open bladder outlet at the end of transurethral incision of the prostate.

CLINICAL OUTCOMES OF TRANSURETHRAL RESECTION OF THE PROSTATE

Treatment Outcomes From Recent Studies on Transurethral Resection of the Prostate

	IPSS		Q_{max}	
Study	***Baseline***	***Postoperative***	***Baseline***	***Postoperative***
Anson *et al.* [1]	18.2	5.1	10.0	21.8
Borboroglu *et al.* [2]	23.8	6.4	ND	ND
Carter *et al.* [3]	19.8	5.9	ND	ND
Cowles *et al.* [4]	20.8	7.5	9.5	16.5
Dixon *et al.* [5]	20.5	7.7	8.8	14.7
Fay *et al.* [6]	22.5	8.6	8.8	18.9
Francisca *et al.* [7]	20.8	3.2	7.9	23.5
Gilling *et al.* [8]	23.0	4.3	9.1	20.4
Kabalin *et al.* [9]	18.8	6.4	9.0	21.2
Kaplan *et al.* [10]	18.3	6.1	8.3	19.6
Karanjavala *et al.* [11]	19.0	4.5	9.5	19.7
Keoghane *et al.* [12]	19.4	6.5	11.4	12.7
Keoghane *et al.* [13]	20.2	7.0	9.0	14.0
Küpeli *et al.* [14]	21.6	5.2	9.2	19.7
Mottet *et al.* [15]	23.7	4.7	7.7	17.6
Muschter *et al.* [16]	21.1	3.5	8.9	25.6
Oesterling *et al.* [17]	24.0	8.6	8.8	20.8
Patel *et al.* [18]	23.3	3.2	7.5	22.6
Uchida *et al.* [19]	21.3	3.3	8.0	21.1

FIGURE 6-12. Treatment outcomes of the transurethral resection of the prostate (TURP) arms of recent studies comparing TURP with minimally invasive treatment modalities demonstrating overall excellent improvements of symptoms and urinary flow rates. IPSS—International Prostate Symptom Score.

Complications of Transurethral Resection of the Prostate

Study	Mortality, %	Morbidity, %	Blood Transfusion, %	Hospital Stay, d
Borboroglu *et al.* [2] (*n* = 520, 1991–1998, 42-mo follow-up, resected weight 18.8 g)	0	2.5 (intraoperative) 10.8 (early postoperative) 8.5 (late) 2.5 (repeat TURP)	0.4	2.4
Uchida *et al.* [20] (*n* = 1941, 1985–1996, resected weight 23 g)	0.05	9.5 (overall)	6.1	
Uchida *et al.* [20] (*n* = 1930, 1971–1985, resected weight 26 g)	0.2	17 (overall)	20	
Fourcade *et al.* [21] (*n* = 410, 1996, resected weight 25.3 g)		8.5 (UTI) 6.5 (urethral stenosis)	2.4	
Mebust *et al.* [22] (*n* = 3885, 1989, resected weight 22 g)	0.1	24.9	6.4	5 (in 78% of patients)
Barba *et al.* [23] (*n* = 1000, 1990–1994, resected weight 37 g)		7.9 (sodium substitution) 8.5 (postoperative revision)	16.5	7.7

FIGURE 6-13. Complications of transurethral resection of the prostate (TURP). UTI—urinary tract infection.

OPEN PROSTATECTOMY: SUPRAPUBIC

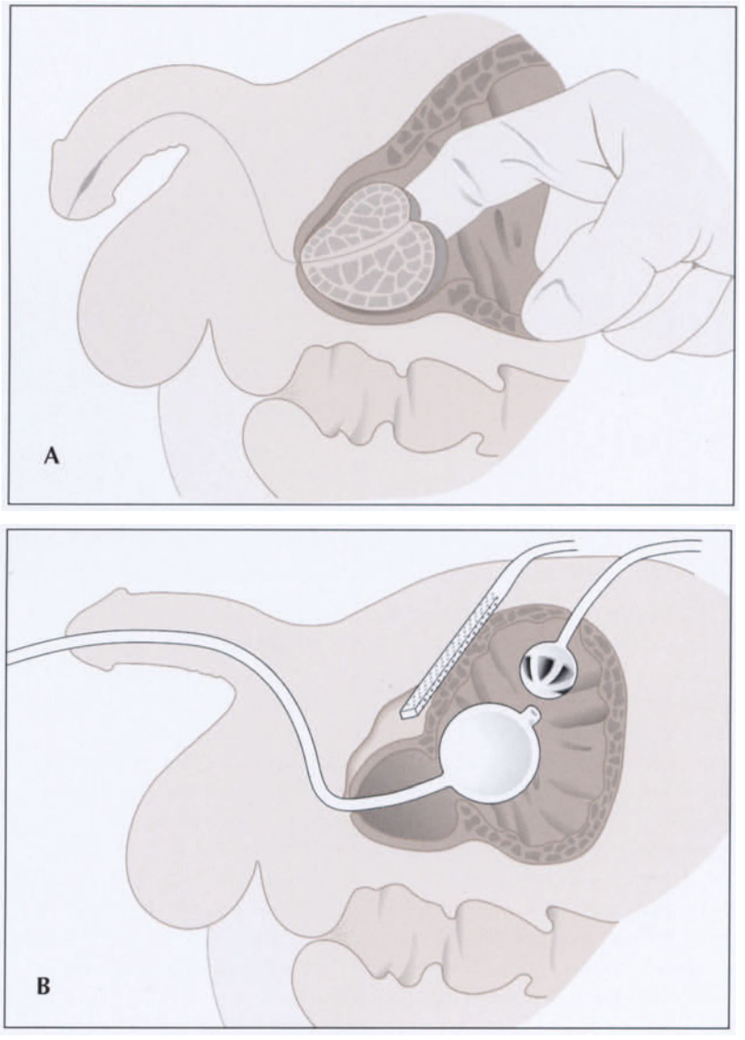

FIGURE 6-14. Blunt enucleation of the prostate. **A,** After skin incision and separation of the muscles in the midline, the retropubic space is exposed. If a wider exposure is needed, the tendinous insertion of the rectus on the pubis can be partially incised and reapproximated at the end of the procedure. Classically, a suprapubic or transvesical prostatectomy is performed through a midline bladder incision. The incision starts just cephalad to the bladder neck. Alternatively, a transverse incision approximately 1 cm above the bladder neck may be used. The combined incision is in the midline of the bladder and extends into the capsule of the prostate. With extension into the muscle of the prostate, it may be necessary to place a deep chromic stitch into the capsule of the prostate to control bleeding from the dorsal vein complex. Blunt enucleation of the prostate is begun by cutting through the anterior commissure of the prostate. The surgeon then finds the plane between the compressed prostatic capsule and the adenoma. Alternatively, the surgeon may incise the mucosa overlying the prostate at the vesical junction and bluntly or sharply find the plane between the adenoma and surgical capsule. The adenoma is then enucleated. The apex can then be pinched off as it meets the prostatic urethra. Care must be taken not to distract the apex cephalad and inadvertently damage the more distal portion of the external sphincter mechanism. If the vertical incision has been extended into the prostatic capsule, the urethra can be divided from the prostate more precisely with better exposure of the area. A warm, moist gauze pack is placed firmly in the prostatic fossa to tamponade venous bleeding after a transvesical prostatectomy. Figure-eight 0 chromic catgut sutures are placed at 5 and 7 o'clock to control bleeding from major arterial branches to the prostate. Bleeding within the fossa is controlled via individual suture ligatures of 3-0 chromic, or, alternatively, bleeding points can be cauterized using the ball electrode. Bleeding from the prostatic fossa may also be controlled by using a pull-out suture of heavy nonabsorbable suture to pursestring the bladder neck. With a pursestring pulled tight to approximate the bladder neck, a Foley catheter is snugged up to the bladder neck.

B, A suprapubic tube (*eg*, 26-F Malecot) is placed through the dome of the bladder after the bleeding is controlled. An indwelling urethral catheter is left to permit through-and-through irrigation to wash out clots. A suction drain (*eg*, Jackson-Pratt) is left in the space of Retzius. The bladder is closed in two layers using 2-0 chromic catgut running suture on the mucosa and interrupted 0 chromic catgut suture on the serosa and muscular area.

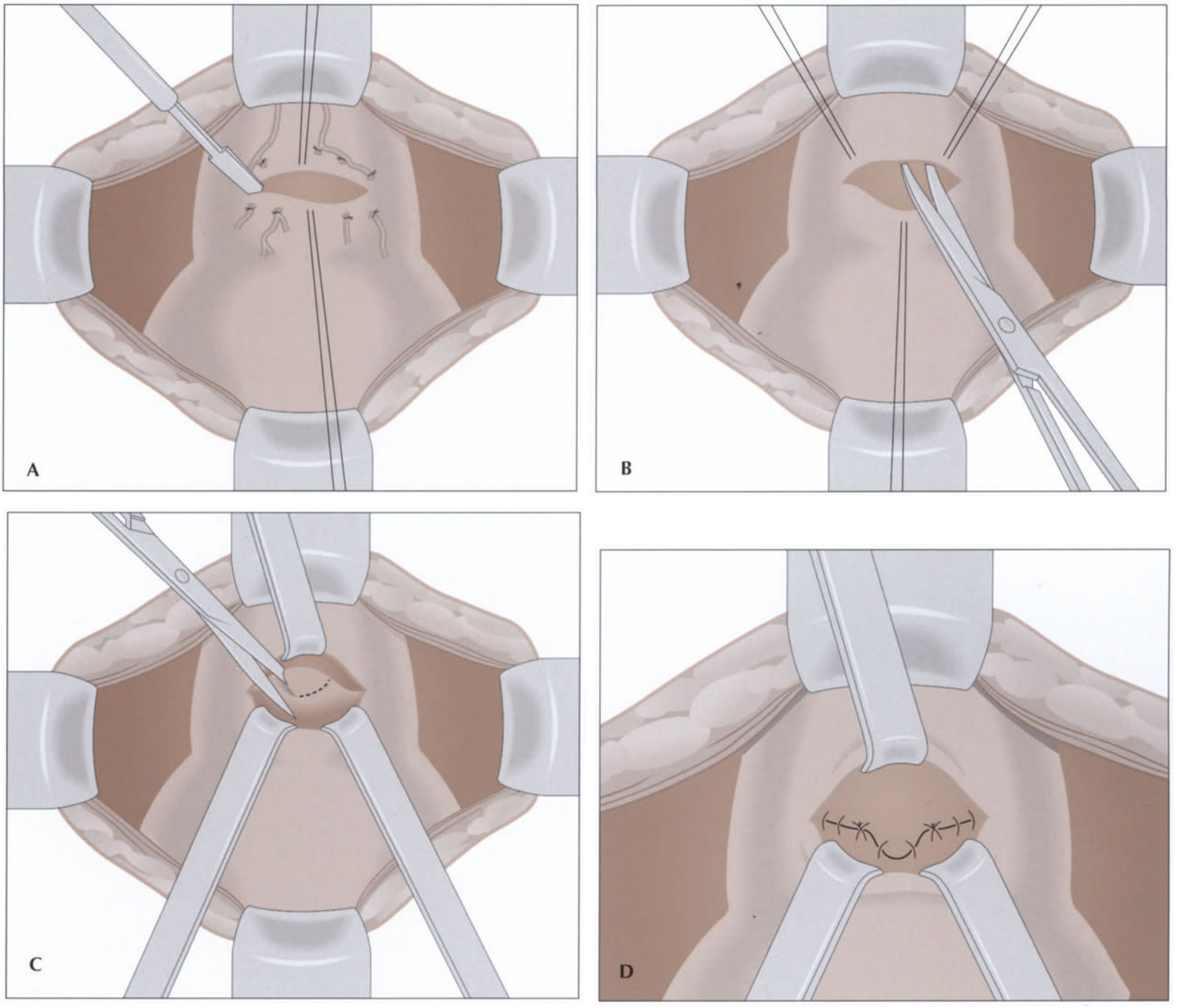

FIGURE 6-15. Schematic representation. **A,** Incision of the prostate capsule. A transverse capsular incision is made through the prostate midway between the apex of the prostate and bladder neck. Stay sutures are used to elevate the surgical capsule, exposing the adenoma. Venous capsular bleeders are suture ligated or cauterized as necessary.

B, Sharp dissection of the adenoma. A plane between the capsule and the adenoma is identified and, using curved scissors, the adenoma is sharply dissected away from the surgical capsule of the prostate. The urethral mucosa attachment can be transected with scissors and careful dissection of the lateral lobes of the prostate accomplished. The adenoma is then grasped with a tenaculum and dissection carried out sharply, removing the adenoma up to the bladder neck. At this point, the mucosa at the bladder neck is sharply incised and the adenoma removed. Figure-eight 0 chromic sutures are placed at 5 and 7 o'clock in the bladder neck to control arterial bleeding.

C, Wedge resection of bladder neck. After retropubic prostatectomy, a V-shaped wedge of bladder neck may be removed if the bladder neck appears to be partially obstructed. **D,** Closure of wedge resection of the bladder neck. After a wedge of bladder neck is removed, the bladder mucosa is advanced over the cut edge and secured to the prostatic fossa. This may prevent a secondary vesical neck contracture. Bleeding within the prostatic capsule is controlled with suture ligatures and cautery as needed. If bleeding is insignificant at this point, a suprapubic tube may be unnecessary. A three-way catheter is inserted into the bladder for continuous irrigation with normal saline in the postoperative period. The capsule of the prostate is closed with interrupted 0 chromic catgut sutures. A suction drain is placed into the retropubic space and brought out through a separate stab wound in the anterior abdominal wall. The abdominal fascia and skin are closed in the usual manner.

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Prostatitis: Definition and Clinical Approaches

7

John N. Krieger

We tell our medical students that the prostate is easy. There are only three problems: 1) prostate cancer (CaP), which is a common cause of death among adult men; 2) benign prostatic hyperplasia (BPH), which is also a common cause of morbidity among adult men and represents an indication for considerable medical and surgical therapy; and 3) prostatitis. Prostatitis also causes considerable morbidity and loss of productivity, and is a frequent cause of visits to physicians in the United States [1–4]. Of the three conditions, prostatitis is by far the least well understood. Perhaps the problem with prostatitis is that we do not have a good abbreviation!

There are several definitions of prostatitis. One of the real problems is that it matters very much which literature one is reviewing. The definition is remarkably different depending on how one approaches this problem. There are different definitions in the pathology literature, in the urology literature, in the infertility literature, and in clinical practice. These definitions include histologic and traditional urologic, based on presence or absence of infection, and the standard clinical definition. The aim of this chapter is to examine many of these definitions and to explain the new consensus classification of prostatitis.

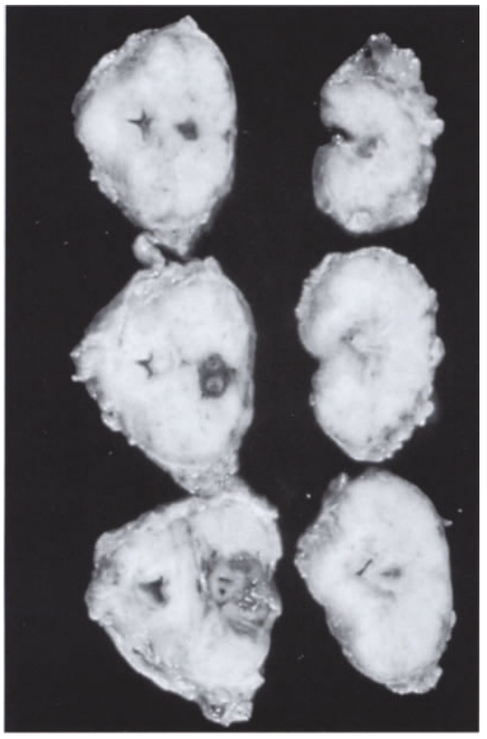


FIGURE 7-1. Step-sections of a "normal prostate" from the bladder base through the urethra. Note that there is a focus of gross inflammation apparent in this specimen, illustrating that areas of pathologic prostatitis are commonly seen in autopsy material.

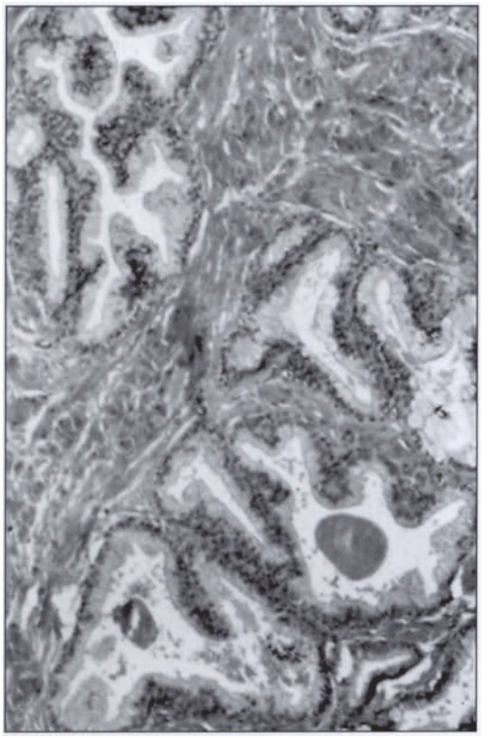


FIGURE 7-2. Normal prostate showing the typical histologic appearance of benign-appearing glands and stroma. Note the corpora amylacea.

Histopathologic Criteria for Prostatitis Diagnosis

Examination of tissue
- Benign prostatic hypertrophy
- Definition and categorization of prostatitis
- Inflammatory infiltrates
  - Presence
  - Characteristics

FIGURE 7-3. Criteria for prostatitis diagnosis. In pathology, diagnosis of prostatitis is based on the histologic picture. Pathologists seldom have access to clinical history, physical examination, or microbiologic findings. Thus, diagnosis of prostatitis by pathologists is based entirely on histopathologic criteria.

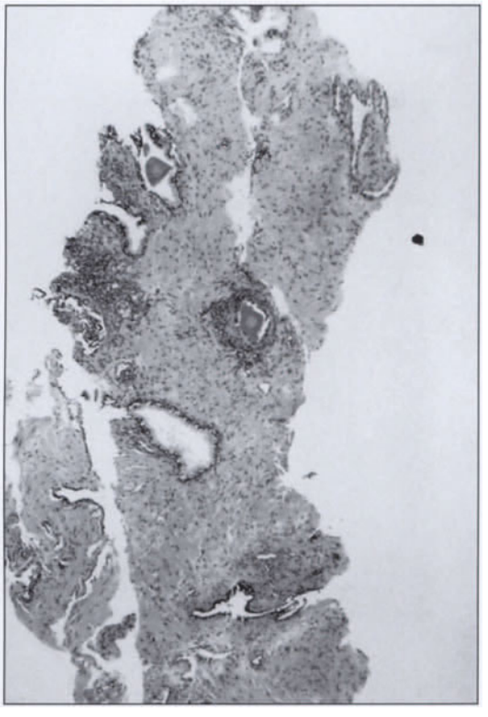


FIGURE 7-4. Typical low-power view of a prostate chip from a transurethral resection specimen showing areas of obvious inflammation. This image represents a very unusual patient from the pathologic perspective—because of the documented clinical history and microbiologic data. The patient is a 67-year-old man with acute urinary tract obstruction due to acute bacterial infection with *Escherichia coli* (>10^6 cfu/mL). Bladder drainage and antimicrobial agents resolved his infection. Unfortunately, he was unable to resume normal voiding. Several weeks later we performed a transurethral resection of the prostate, which resolved his bladder outflow obstruction.

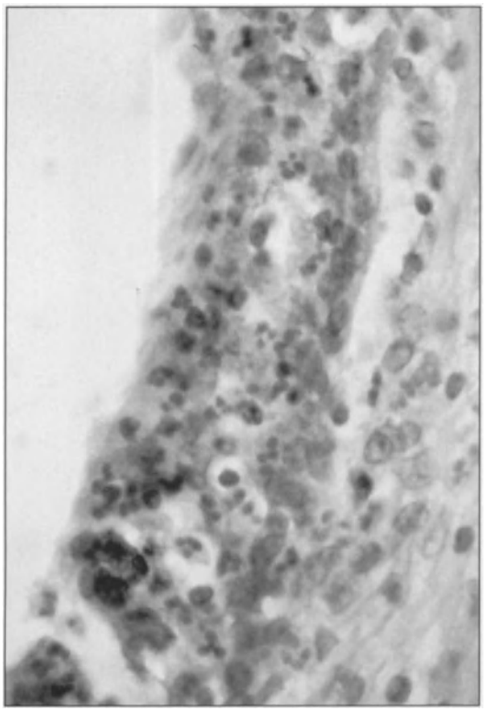


FIGURE 7-5. High-power view showing an acute inflammatory infiltrate. The pathologic diagnosis was acute prostatitis.

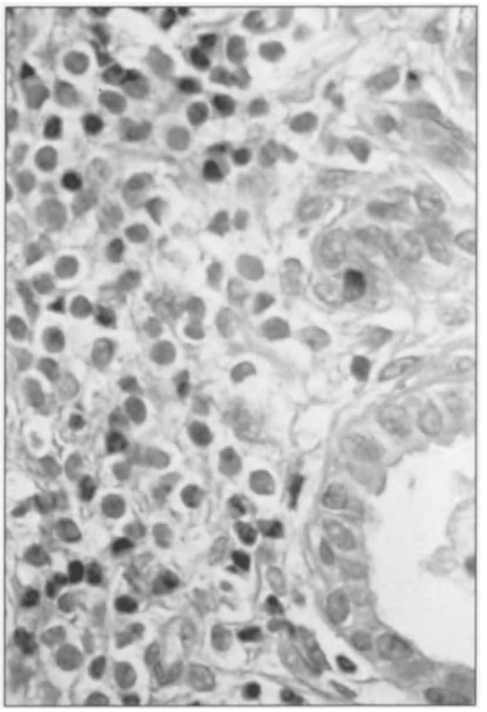


FIGURE 7-6. Another case with a chronic inflammatory infiltrate. The pathologic diagnosis was chronic prostatitis.

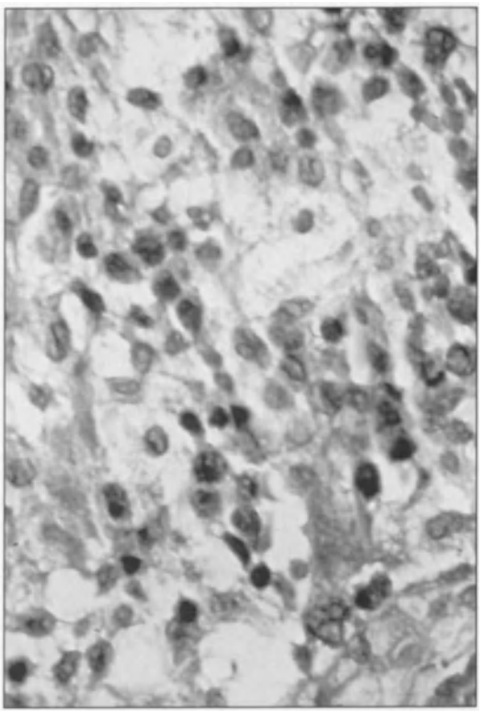


FIGURE 7-7. A case of eosinophilic prostatitis with characteristic red-staining eosinophils predominating in the inflammatory infiltrate. These cases are often associated with allergic reactions.

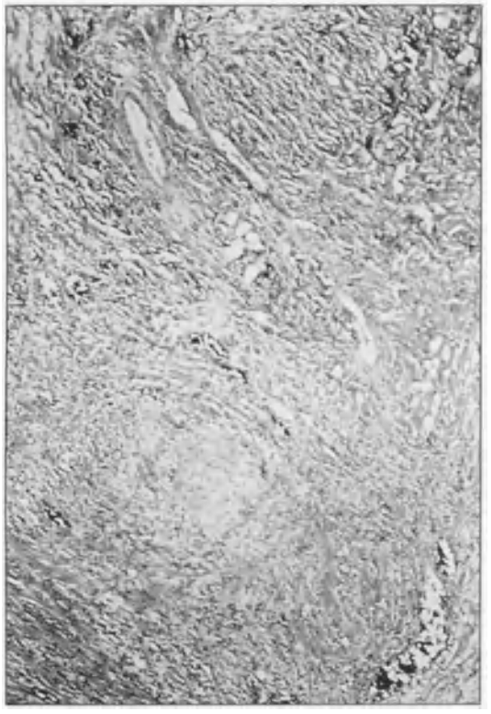


FIGURE 7-8. Pathologic diagnosis of granulomatous prostatitis. Granulomatous prostatitis is the characteristic histologic reaction of the prostate to a variety of different causes. Many cases are idiopathic, including this one.

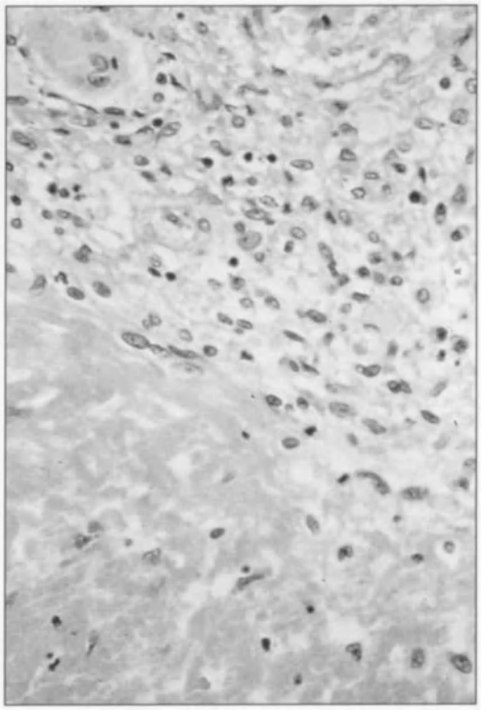


FIGURE 7-9. Granulomatous prostatitis due to tuberculosis. Other cases of granulomatous prostatitis are related to urologic surgery or to specific infections, such as tuberculosis, bacille Calmette-Guérin therapy, or fungal infections. Note the caseous necrosis and Langerhan's giant cells.

Problems with the Pathologic Definition and Classification of Prostatitis

Population
Inflammation or infection may be focal
Not well correlated with clinical findings
Many men with no history of prostatitis have histologic findings of prostatitis

FIGURE 7-10. Problems with the pathologic definition and classification of prostatitis. First, the population studied is approximately 20 years older than the typical population of patients with symptoms of chronic prostatitis. Second, step-sections of prostates removed at autopsy show that inflammation and infection may be focal, affecting some areas of the prostate but not other areas. Third, the pathologic diagnoses and findings have not been well correlated with clinical findings. In the older literature, pathology has rarely been found to be helpful in the clinical management of patients with prostatitis symptoms. Fourth, in our practice many men with no history of prostatitis who undergo prostatectomy for benign or malignant disease have histologic findings of prostatitis.

Prostate Histopathology in Chronic Prostatitis

Study	*Patients, n*	*Prostate Biopsies, n*	*Patient Characteristics*
True *et al.* [5]	97	368	All had symptoms of chronic prostatitis Negative evaluation for infection Negative clinical evaluation

FIGURE 7-11. Results of a recent study on prostate histopathology in chronic prostatitis [5]. Recent studies demonstrate another fundamental problem with the pathological definition of prostatitis [5]. This study evaluated more than 368 transperineal prostate biopsy specimens from 97 patients with symptoms of chronic prostatitis. None of these patients had evidence of infection following an extensive microbiologic evaluation. None had evidence of structural or functional abnormalities of the lower genitourinary tract. The surprising finding was that only 38% of these patients had inflammation in their prostate biopsies. Further, of the patients with histologic evidence of inflammation, most had only modest inflammatory infiltrates.

The Traditional Definition of Prostatitis

Meares-Stamey (research definition)
  Lower urinary tract localization
  VB1, VB2, EPS, VB3 (cultures or microscopy)
Four clinical syndromes
  Acute bacterial prostatitis
  Chronic bacterial prostatitis
  Nonbacterial prostatitis
  Prostatodynia

FIGURE 7-12. The traditional definition of prostatitis. The traditional definition used in the urology literature has been based on the Meares-Stamey definition and classification [6–8]. This research definition is based on careful lower urinary tract localization studies, which include examination of the following: VB1 (voided bladder 1 or first-void urine), VB2 (voided bladder 2, or midstream urine), expressed prostatic secretions (EPS), and VB3 (voided bladder 3, or postmassage urine), using quantitative cultures and microscopy. The four clinical syndromes that have classically been described are listed in this figure.

Distinctions Among the Four Clinical Syndromes of Prostatitis

Syndrome	*Symptoms*	*EPS Leukocytes*	*Bacteriuria*	*Physical Examination*
Acute bacterial	+	+	+	+
Chronic bacterial	+	+	+	
Nonbacterial	+	+		
Prostatodynia	+			

FIGURE 7-13. Distinctions among the four clinical syndromes of prostatitis. Acute bacterial prostatitis is associated with characteristic symptoms of acute urinary tract infection. On occasion, the patient may be septic and present with a systemic illness. The physical examination is frequently impressive with local bladder tenderness, an exquisitely tender and tense prostate on rectal examination, and occasionally signs of systemic infection. The patient has bacteriuria defined as presence of uropathogens in the midstream urine. The expressed prostatic secretions (EPS) have leukocytes and pathogenic bacteria.

Chronic bacterial prostatitis is characterized by recurrent symptoms of acute urinary tract infection. There are increased numbers of leukocytes in the prostatic secretions, and uropathogens are present episodically in the midstream urine. The physical examination may or may not be impressive. The characteristic clinical feature of chronic bacterial prostatitis is recurrent urinary tract infections caused by the same bacterial species.

In contrast, nonbacterial prostatitis and prostatodynia are not associated with bacteriuria. These patients are symptomatic. The distinction between nonbacterial prostatitis and prostatodynia is based on the presence of increased numbers of EPS leukocytes in patients with nonbacterial prostatitis, but not in patients with prostatodynia.

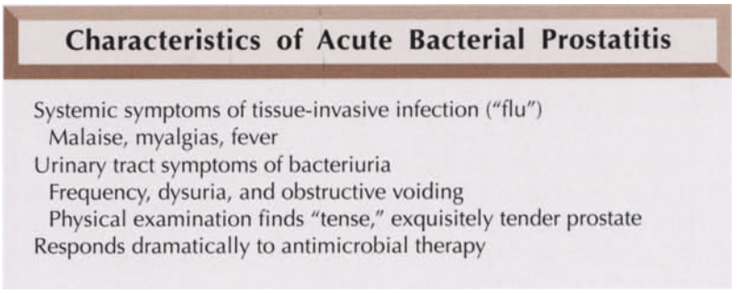


FIGURE 7-14. Characteristics of acute bacterial prostatitis. Acute bacterial prostatitis is associated with systemic symptoms of a tissue-invasive infection. The patient may present with a flu-like syndrome characterized by malaise, myalgias, and fever. The patient will have urinary tract symptoms of bacteriuria characterized by increased urinary frequency, dysuria, and often obstructed voiding. On physical examination the prostate may be "tense" and exquisitely tender. Fortunately, these patients respond dramatically to appropriate antimicrobial therapy for recognized uropathogens. Many agents that do not get into the prostate under noninflamed conditions work very well in this syndrome. This is usually not a difficult or subtle diagnosis.

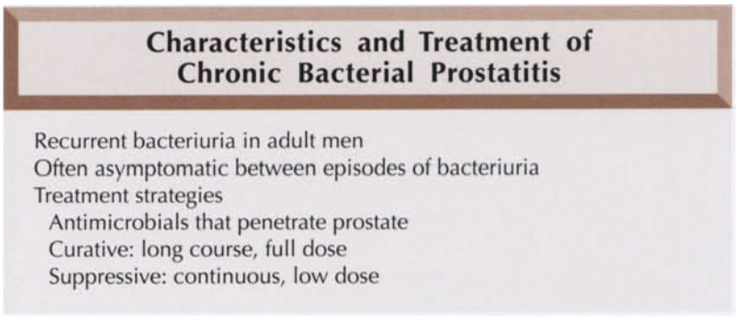


FIGURE 7-15. Characteristics of chronic bacterial prostatitis. Chronic bacterial prostatitis is the most common cause of recurrent bacteriuria in adult men. It is noteworthy that these patients may be totally asymptomatic between acute episodes of bacteriuria.

There are a number of treatment strategies using antimicrobial agents that penetrate the prostatic parenchyma. One can use curative treatment strategies, meaning a long course (in my practice, 6 weeks to 3 months) of full-dose antimicrobial therapy, usually using a drug such as fluoroquinolone or trimethoprim-sulfamethoxazole. This regimen will cure 30% to 50% of patients. For patients who cannot be cured, one can use a strategy of suppression with continuous low-dose therapy using nightly or every-other-night dosing of a low-dose agent to suppress bladder bacteriuria. This is the US Food and Drug Administration's definition of prostatitis, but it represents very few patients seen in clinical practice.

Diagnosis Localization Cultures in Some Cases of Chronic Bacterial Prostatitis

Organism	*VB1*	*VB2*	*EPS*	*VB3*
Escherichia coli	1200	1200	15,000	4400
E. coli	0	0	4000	110
E. coli	100	200	2700	110
E. coli	240	140	2700	270
E. coli	0	0	100	0
Pseudomonas aeruginosa	0	0	50,000	300
Enterobacter cloacae	0	0	1500	10

FIGURE 7-16. Diagnostic localization cultures in some cases of chronic bacterial prostatitis [9]. In each case the patient had recurrent episodes of bacteriuria caused by the same organism that we localized to the prostate using the four-glass test. Many of these patients required more than one study for definitive localization. Note that these organisms are all recognized uropathogens. These seven patients all had gram-negative rod infections. It is possible to have a gram-positive result, but it is important to document recurrent episodes of bacteriuria caused by that organism. The characteristic localization pattern is a 10-fold increase when the VB3 sample is compared with the VB1 sample. If that criterion fails, one can compare the expressed prostatic secretion (EPS) sample with the VB1. VB1—voided bladder 1; VB2—voided bladder 2; VB3—voided bladder 3.

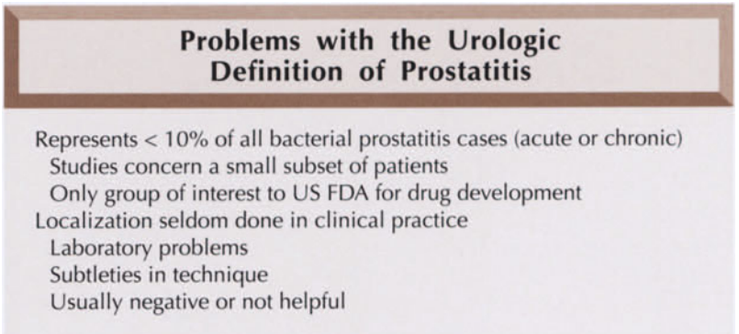


FIGURE 7-17. Problems with the urologic definition of prostatitis. First and foremost, this definition represents less than 10% of bacterial prostatitis seen in clinical practice. Much of the literature concerns a very small subset of highly selected patients. Localization studies, although described very carefully and thoroughly in research settings, are seldom done in clinical practice. This is for a number of reasons, such as problems setting up the laboratory studies and subtleties in technique. However, most clinicians believe that these studies are usually negative and thus are not particularly helpful or cost-effective for most patients. US FDA—US Food and Drug Administration.

Assumptions Made by the Traditional Definition

Nonbacterial prostatitis indicates a physical problem
- Fastidious microorganisms
  - (many classified as bacteria, *eg, Chlamydia trachomatis*)

Inflammatory disorder (noninfectious)
Allergy
Stones
Other organic pathology

FIGURE 7-18. Assumptions implicit in the traditional urologic definition of prostatitis. The first is that patients with nonbacterial prostatitis have a physical problem, such as the presence of fastidious microorganisms. Many of these potential organisms are classified as bacteria, such as *Chlamydia trachomatis* [9].Thus, nonbacterial prostatitis is in fact a misnomer. Others have suggested that nonbacterial prostatitis is an inflammatory disorder that may be noninfectious [10]. Other theories in the literature are that nonbacterial prostatitis is related to allergy, prostate stones, a variant of interstitial cystitis, or other organic pathology, such as voiding dysfunction or reflux of sterile urine into the prostatic ducts [10–17].

Causes of Prostatodynia

Neuromuscular: genitourinary diaphragm
- "Pelvic floor tension myalgia"

Primary voiding disturbance
- Bladder neck obstruction
- External sphincter spasm
- Treatment includes TURP, TUIP, cystoprostatectomy, hyperthermia, diazepam, α-blockers

Primary psychologic disturbances

FIGURE 7-19. Prostatodynia. The syndrome of prostatodynia has been ascribed to a variety of causes, such as neuromuscular dysfunction of the genitourinary diaphragm. Some suggest that this is "pelvic floor tension myalgia" [10]. Others suggest that this is a primary voiding disturbance with abnormalities at the bladder neck or external sphincter spasm. Treatment recommendations include transurethral resection or incision of the prostate. Other procedures described in the recent literature include cystoprostatectomy, hyperthermia, and use of α-blockers. Such treatments may help some patients, although our clinic is full of patients in whom such therapies failed. Still other authors suggest that there is a primary psychologic disturbance in these patients, and that "psychiatric counseling should be seriously pursued, because these patients have serious personality disturbances and defects in sexual identification" [7]. TUIP—transurethral incision of the prostate; TURP—transurethral resection of the prostate.

Experiential Findings Regarding Prostatitis and Prostatodynia

Symptoms similar in nonbacterial prostatitis and prostatodynia
EPS findings variable
Fastidious organisms isolated from both populations
Both groups are often frustrated, depressed
- Psychologic abnormalities common among patients with chronic diseases associated with pain
- Gastric ulcer and *Helicobacter pylori*

FIGURE 7-20. Experiential findings regarding prostatitis and prostatodynia. In our experience, symptoms are often similar in patients with nonbacterial prostatitis and prostatodynia. Further, findings in the prostatic fluid of individual men may be variable [13]. We have isolated fastidious organisms from both populations. Both groups of men are often frustrated and depressed [14,15]. Their quality of life is impaired substantially [16]. However, psychologic abnormalities are very common among patients with chronic diseases associated with pain, and one must not forget that gastric ulcer, once ascribed to personality disorders, now is recognized as an infectious disease. EPS—expressed prostatic secretion.

Another Definition of Prostatitis Based on the Fertility Literature

Seminal fluid analysis
Various terms in addition to prostatitis
- Leukocytospermia
- Pyosemia
- Prostatoseminal vesiculitis
- Epididymo-prostato-vesiculitis
- Male accessory gland infection
- Seminal inflammation (preferred)

FIGURE 7-21. Still another definition of prostatitis is used in the fertility literature. This definition is based on identification of inflammation in the seminal fluid. Various terms are used in this literature in addition to prostatitis [17].

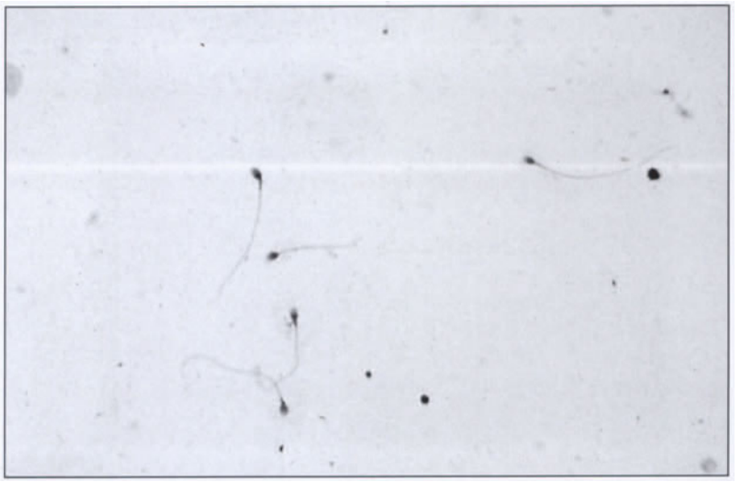


FIGURE 7-22. A normal seminal fluid specimen that has been stained with Papanicolaou stain. Sperm and a few leukocytes are shown.

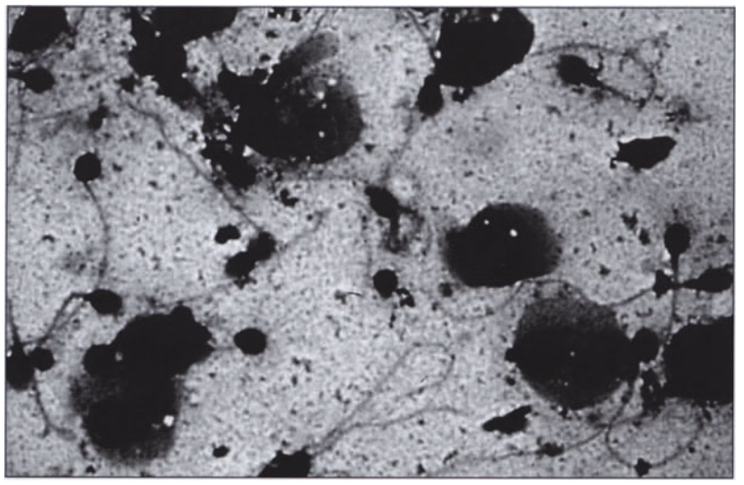


FIGURE 7-23. A seminal fluid sample with increased numbers of polymorphonuclear leukocytes. Note that the slide is stained with Bryan-Leishman's stain to facilitate differentiation of leukocytes from sperm forms. Cells with pink cytoplasm are leukocytes, whereas cells with gray cytoplasm are germ cells.

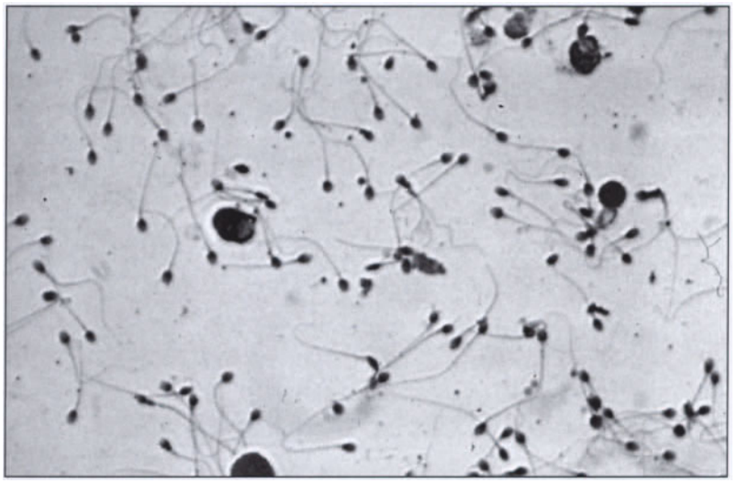


FIGURE 7-24. A monoclonal antibody-stained preparation (HLe1), illustrating that the inflammatory cells are indeed leukocytes.

Problems with the Andrology Definition of Prostatitis

Population studied
Methods
  Staining: distinguish leukocytes from sperm
  Definition of inflammation
    > 10^6 leukocytes per milliliter of semen
    > 6 leukocytes per 100 sperm
Possible relationship of leukocytospermia to:
  Infection
  Infertility

FIGURE 7-25. Problems with the andrology definition of prostatitis. The first problem is the populations studied, which are predominantly patients with infertility as their chief complaint, not prostatitis. A second problem concerns the methods. Many studies used "round cell" counts in unstained specimens. Staining is necessary to distinguish leukocytes from sperm. Third, there have been varying definitions of inflammation (numbers or concentrations of leukocytes) used in this literature. Fourth, the question of the relationship between leukocytospermia and either infection or infertility is incompletely defined.

Other problems include the fact that leukocytes in semen can come from multiple sites besides the prostate. Most studies in this literature, however, seldom evaluate other sites, such as the urethra or expressed prostatic secretions, for presence of inflammation. Many studies lack data on patients' symptoms or physical findings. Finally, limited data correlate seminal fluid analysis findings with either findings in the prostatic secretions or with histology of the prostate.

Standard Clinical Definition of Prostatitis

Based on symptoms
Limited laboratory evaluation
Repeated courses of empirical therapy

FIGURE 7-26. The clinical definition of prostatitis. Stamey [7] describes this definition as "a wastebasket of clinical ignorance used to describe any condition associated with prostatic inflammation or prostatic symptoms . . . most commonly diagnosed in patients who have no history of bladder infection despite the presence of perineal aching, low back pain, or urinary discomfort."

The standard clinical definition of prostatitis is based entirely on symptoms. Most patients undergo limited laboratory evaluation. In contrast, they have repeated courses of empirical therapy using a variety of agents. This does have one overriding advantage: the clinical definition does address what patients actually suffer from.

Genitourinary Symptoms of Chronic Prostatitis

General agreement in literature
  Certain pain symptoms common, *ie*, perineal, back, and genital
Marked disagreement regarding:
  Voiding complaints
  Sexual dysfunction

FIGURE 7-27. The genitourinary symptoms of chronic prostatitis. Careful review of the literature found general agreement on the presence of certain pain symptoms, such as perineal, back, and genital pain [18]. However, there was marked disagreement on the prevalence of voiding complaints and sexual dysfunction.

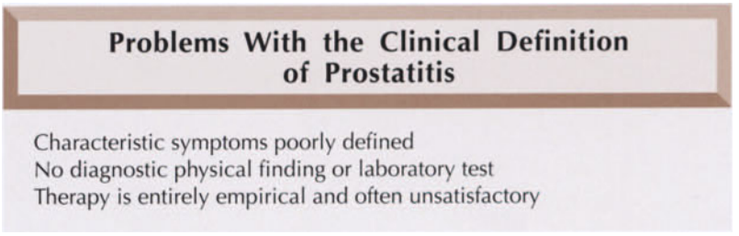


FIGURE 7-28. Problems with the clinical definition of prostatitis. The model used for benign prostatic hyperplasia (BPH) may prove valuable. In the new BPH model, the American Urological Association symptom score proved critical for developing new therapies, although we still do not completely understand the cause of BPH.

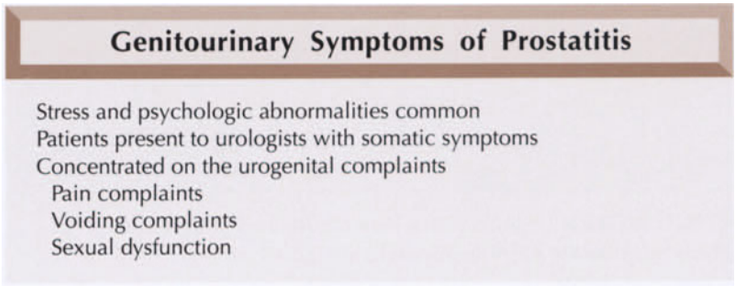
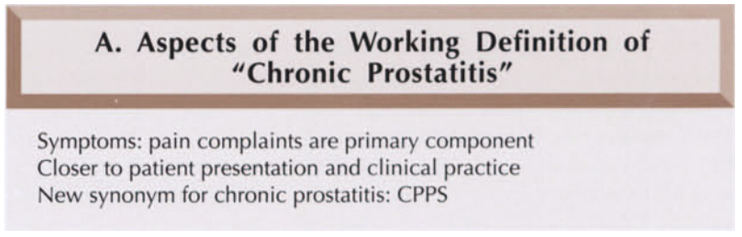


FIGURE 7-29. Genitourinary symptoms of prostatitis. What we do know about the genitourinary symptoms of prostatitis is that stress and psychologic abnormalities are very common. Many of these patients present to urologists with somatic symptoms; therefore, we and others have concentrated on developing instruments that evaluate the genitourinary complaints of these patients. We found that most complaints can be classified as either pain complaints, voiding complaints, or sexual dysfunction complaints [18]. To summarize, prostatitis causes considerable morbidity. It is neglected in terms of research and new clinical initiatives compared with the other prostate diseases. Although there are at least four definitions, none of them work well for the great majority of patients.



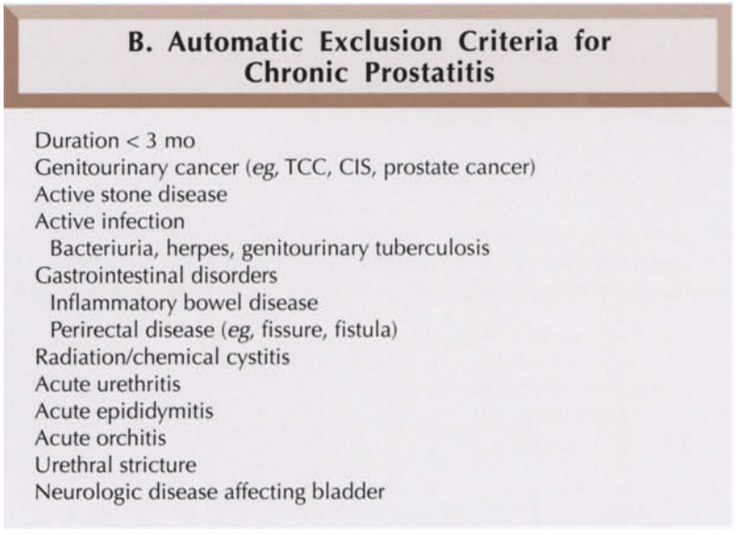


FIGURE 7-30. Consensus working definition of "chronic prostatitis." As a first step in addressing these problems, a new working definition for chronic prostatitis was developed by an expert panel convened by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [19]. **A,** This new definition, which has yet to be validated, concentrated on patients' symptoms using pain complaints as a primary component. In this respect it is much closer to patient presentation and clinical practice. In addition there is a new synonym for chronic prostatitis: chronic pelvic pain syndrome (CPPS).

B, Exclusion criteria. These criteria include duration less than 3 months, presence of genitourinary cancers such as transitional cell carcinoma (TCC), carcinoma in situ (CIS), or carcinoma of the prostate. Other exclusions include presence of active stone disease, because a distal ureteral stone or crystaluria can cause lower tract symptoms. Presence of active infection, such as bacteriuria, herpes, or genitourinary tuberculosis, presence of genitourinary disease, such as inflammatory bowel disease or perirectal disease such as fissure or fistula, also exclude patients from the NIDDK definition. Other automatic exclusions are also listed in this figure.

A. Symptomatic Prostatitis Syndromes

Bacterial prostatitis
- Acute and chronic

Chronic prostatitis
- CPPS or "abacterial" prostatitis

B. Aspects of Acute and Chronic Bacterial Prostatitis

Acute
- Bacteriuria
  - Uropathogens
- Possible systemic illness

Chronic
- Recurrent episodes of bacteriuria
- Organism "localizes" to prostate

C. Chronic Prostatitis or Chronic Pelvic Pain Syndrome

Inflammatory
- Leukocytes in EPS, semen, VB3

Noninflammatory
- No leukocytes

FIGURE 7-31. Prostatitis syndromes. The National Institute of Diabetes and Digestive and Kidney Diseases consensus classification of prostatitis considers prostatitis syndromes as either symptomatic or asymptomatic. **A,** The symptomatic prostatitis syndromes include bacterial prostatitis, either acute or chronic, and chronic prostatitis or chronic pelvic pain syndrome (CPPS), also known as "abacterial" prostatitis. **B,** Aspects of acute and chronic bacterial prostatitis. Acute bacterial prostatitis is characterized by presence of bacteriuria caused by recognized uropathogens. Some patients may have a systemic illness. The hallmark of chronic bacterial prostatitis is recurrent episodes of bacteriuria caused by the same organism that localizes to the prostate on segmented cultures. **C,** The third syndrome is chronic prostatitis or chronic pelvic pain syndrome, which has an inflammatory subtype, characterized by presence of leukocytes in prostatic secretions, semen, or postmassage urine, and a noninflammatory subtype, characterized by absence of leukocytes. EPS—expressed prostatic secretions; VB3—voided bladder 3.

Characteristics of Asymptomatic Inflammatory Prostatitis

Increased PSA level
Histology indicates prostatitis
Infertility is only symptom

FIGURE 7-32. Asymptomatic inflammatory prostatitis. Finally, there is a category termed "asymptomatic inflammatory prostatitis." For example, an asymptomatic patient presents with an increased prostate-specific antigen (PSA) and this leads to a biopsy. The most common noncancer diagnosis is prostatitis. There are also patients with infertility, who have no symptoms other than their infertility, and have prostatitis based on seminal fluid findings. Such patients are characterized as having asymptomatic inflammatory prostatitis.

The New Consensus Classification of Prostatitis Syndromes

Acute bacterial prostatitis
Chronic bacterial prostatitis
Chronic prostatitis or CPPS
- Inflammatory
- Noninflammatory

Asymptomatic inflammatory prostatitis

FIGURE 7-33. Summary of the new classification of prostatitis syndromes. CPPS—chronic pelvic pain syndromes.

A. Outline of the National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI)

Nine questions
Four domains
- Pain or discomfort: four items
- Urination: two items
- Impact of symptoms: two items
- Quality of life: one item

Total score

B. NIH-CPSI Pain and Discomfort Scale

In the last week, have you experienced any pain or discomfort in the following areas:
- Perineum
- Testicles
- Tip of penis
- Below the waist, in your pubic or bladder area

In the last week, have you experienced:
- Pain or burning with urination
- Pain or discomfort during or after sexual climax

C. NIH-CPSI Frequency of Pain and Discomfort Scale

How often have you had pain or discomfort in any of these areas over the past week? (0–5 scale)
Which number best describes your *average* pain or discomfort on the days that you have had it, over the last week? (0–10 scale)

FIGURE 7-34. The National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI). To help provide a tool for patient evaluation and development of clinical protocols, a symptom index was developed and validated [20]. **A,** Outline of the NIH-CPSI. The symptom index consists of nine questions (items) covering four domains Thus, it is possible to calculate a total score and scores for each domain. **B,** The pain or discomfort domain evaluates presence of pain in several locations and during urination and during or after ejaculation. **C,** The frequency that patients experience pain or discomfort and the average pain or discomfort level.

(*Continued on next page*)

D. NIH-CPSI Urination Scale

How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week? (0–5 scale)
How often have you had to urinate again < 2 h after you finished urinating, over the last week? (0–5 scale)

E. NIH-CPSI Impact of Symptoms Scale

How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week? (0–3 scale)
How much did the patientdo you think about your symptoms, over the last week? (0–3 scale)

F. NIH-CPSI Quality of Life Scale

If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that? (0–6 scale)

FIGURE 7-34. *Continued* **D,** Urination scale. The urination scale contains two items that evaluate the sensation of bladder emptying and the need to urinate again within 2 hours of the previous micturition. **E,** Impact of symptoms scale. This scale contains two items that evaluate how much the patient's symptoms kept him from doing his usual activities and how much he thinks about his symptoms. **F,** Quality of life scale consists of one item. The combination of the consensus classification for prostatitis syndromes with the NIH-CPSI instrument has provided a new framework for patient evaluation and assessment of symptoms.

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Clinical Aspects of Prostate Cancer

8

Marc S. Ernstoff

An understanding of the gross anatomic relationship of the prostate to other structures within the male pelvis is of great medical importance. Because benign prostatic hyperplasia and adenocarcinoma of the prostate are common conditions of aging men, a clear understanding of the anatomic relationships among the prostate, seminal vesicles, and bladder is important for developing the concepts necessary to understand the clinical aspects and management of early stage prostate cancer.

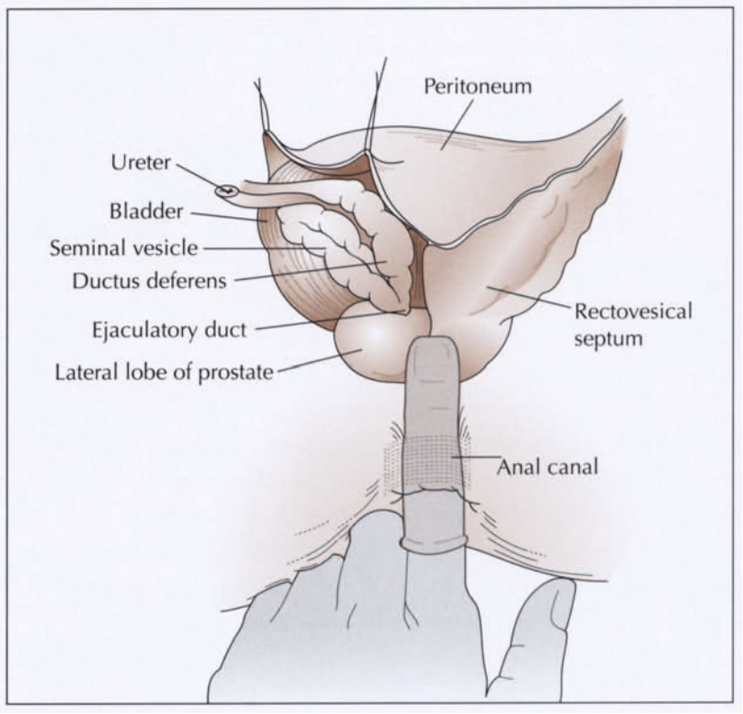


FIGURE 8-1. Digital rectal palpation of the prostate. The prostate is the largest of the male sex accessory glands. It consists of glandular and fibromuscular elements. Normally, the prostate is the size of a horse chestnut or a walnut (≈ 20 g). It is found low in the male pelvis, above the rectum and below the pubis, situated between the bladder superiorly and the urethra inferiorly. It surrounds a major portion of the urethra. The prostate is enclosed by a dense sheath of fascia known as the endopelvic fascia of the prostate. On its anterior surface, the prostate is enveloped in a vast network of venous channels (the prostatic venous plexus), which are responsible for the majority of blood loss during radical removal of the prostate. Blood supply to the prostate emanates primarily from the internal pudendal, the inferior vesicle, and the middle rectal arteries. The lymphatic drainage of the prostate terminates primarily in the internal iliac and sacral lymph nodes. Nerve supply to the prostate emanates from the inferior hypogastric plexus and travels in close approximation with the neurovascular bundle that contains the nerves essential for erectile function. The seminal vesicles, situated at the base of the bladder and anterior to the rectum, are attached to the base of the prostate at the site of entry of the ejaculatory duct. During radical removal of the prostate for prostate cancer, these structures are removed intact with the prostate. This figure demonstrates how the prostate can be palpated rectally. The anterior wall of the rectum and the rectovesicle septum separate the examiner's finger from the posterior surface of the prostate. In some instances, the seminal vesicles can be palpated per the rectum. (*Adapted from* Laurenson [1].)

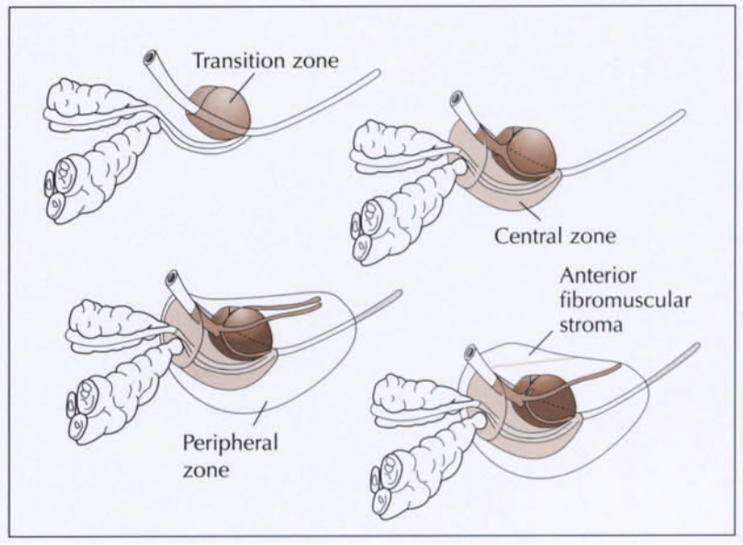


FIGURE 8-2. Surgical anatomy. The glandular structure of the prostate can be divided into three zones. The peripheral zone (PZ) includes 70% of the glandular elements, primarily at the apical, posterior, and lateral region; the central zone surrounds the ejaculatory ducts (20% of glandular elements); and the transition zone (TZ) surrounds the proximal urethra (10% of glandular elements). The anterior fibromuscular stroma, a zone with few glandular elements, extends from the bladder neck (base of the prostate) to the striated urethral sphincter (apex of the prostate). Benign prostatic hyperplasia (BPH) develops in the TZ. In greater than 80% of cases, prostate cancer arises in the PZ and is often multifocal and bilateral. The PZ location of most cancers accounts for the lack of urination symptoms and their accessibility through digital rectal examination. Removal of centrally located TZ tissue for BPH does not remove the area at highest risk for development of prostate cancer. The TZ is the predominant location of the tumor in less than 20% of cases. TZ cancers tend to behave differently than PZ cancers of similar size. TZ cancers may have a lower metastatic biology and are more likely to be confined because of natural barriers to extension (*eg*, urethra, anterior fibromuscular stroma, and fibrous plane between transition and peripheral zone), and, perhaps, a lower biologic potential. Common sites of extraprostatic extension for TZ cancers are the anterolateral gland and bladder neck. (*Adapted from* Greene *et al.* [2].)

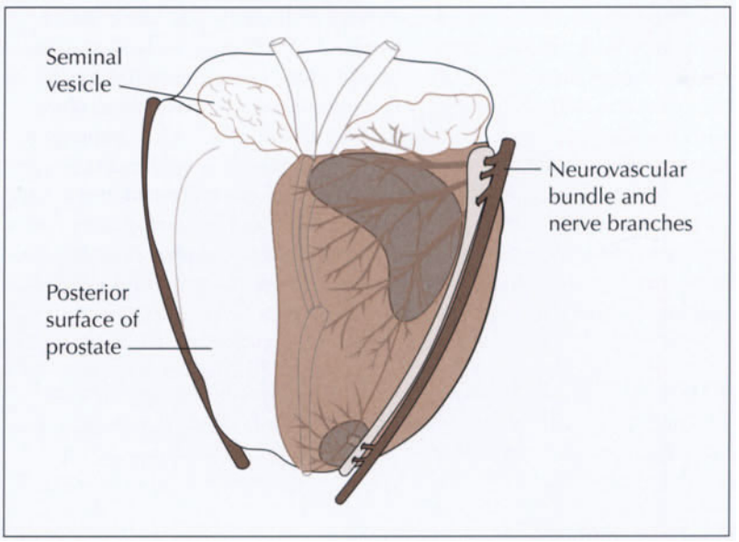


FIGURE 8-3. Posterolateral surface of the prostate gland. Branches of the neurovascular bundles (NVB) enter the prostate on the posterolateral surface. Peripheral zone cancers commonly invade through the perineural space and extend locally posteriorly and posterolaterally via branches of the neurovascular bundle. More extensive extraprostatic extension may involve the seminal vesicles at the base of the prostate. Lymphatic spread of prostate cancer most commonly affects the pelvic lymph nodes surrounding the iliac vein and within the obturator fossa. Hematogenous dissemination of prostate cancer to bone is common (typically the pelvis and lower spine) and less frequently spreads to lung and other organs. (*Adapted from* Stamey and McNeal [3].)

EARLY DETECTION OF PROSTATE CANCER

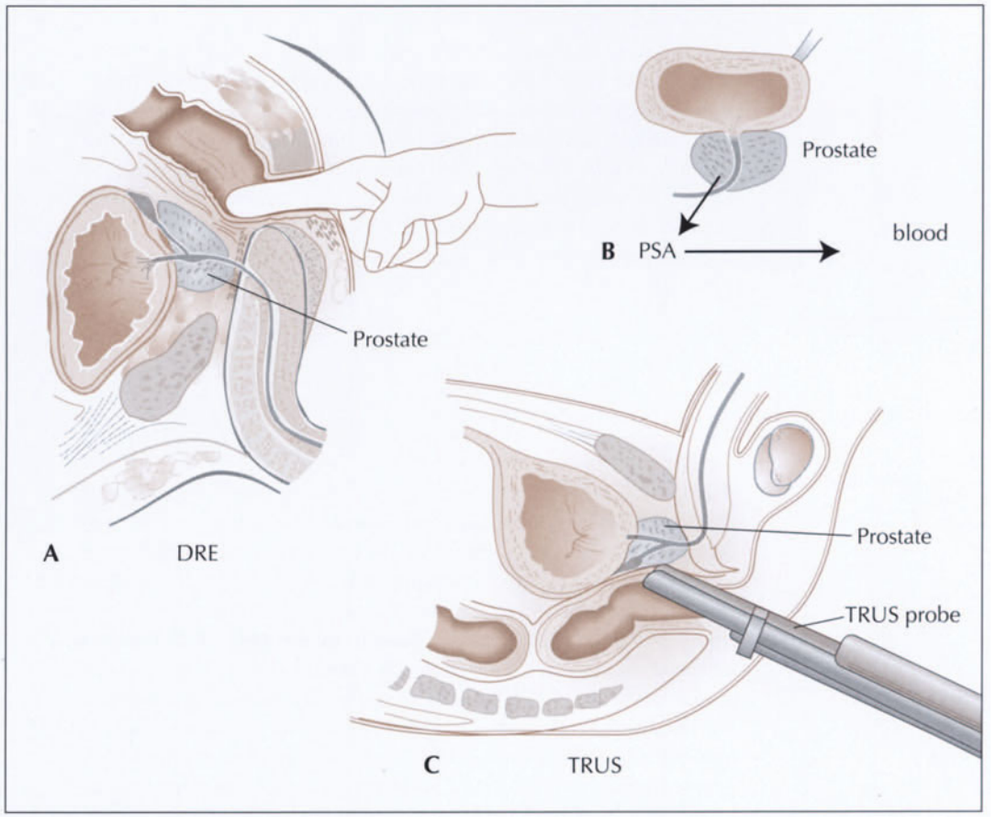


FIGURE 8-4. Diagnostic triad for early detection of prostate cancer. Digital rectal examination (DRE), measurement of the protein prostate-specific antigen (PSA) in sera, and transrectal ultrasound (TRUS)–directed prostatic biopsy comprise a diagnostic triad for early detection of prostate cancer. **A**, DRE usually is performed with the patient bent at the waist 90° over the examining table, feet spread about 2 feet apart, and knees slightly bent. The normal prostate should have the consistency of the thenar eminence of the thumb when the thumb is apposed to the little finger. Prostate cancer should be suspected when the consistency is firmer than normal, or distinct nodules are present. **B**, PSA is a member of the kallikrein family of serine proteases that is important in liquidification of the ejaculate. It can be detected in sera by immunoassay and most commonly is elevated in the presence of prostate disease that occurs with age. **C**, TRUS is performed, with the patient on his side, by gently inserting an ultrasound probe into the rectum. Prostate biopsies can be visually directed using a biopsy gun loaded onto the TRUS probe.

Although controversy exists regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA as first-line tests to assess the risk of prostate cancer being present. When DRE and PSA are used to detect prostate cancer, detection rates are higher with PSA alone than with DRE alone, and highest with a combination of the two tests. Because DRE and PSA do not always detect the same cancers, the tests are complementary. TRUS is not recommended as a first-line screening test because of its low predictive value for early prostate cancer and the high cost of the examination. TRUS-guided, systematic needle biopsy currently is the most reliable method to ensure accurate sampling of prostatic tissue in those men at high risk for harboring prostatic cancer based on DRE abnormalities or PSA elevations. Magnetic resonance imaging for screening is under evaluation and ultimately may have a benefit in subsets of patients with high PSA levels. The introduction of positron emission tomography (PET) scanning is yet unproven in early detection of prostate cancer. The use of carbon-11-choline and N-(3-[18F]fluoropropyl)putrescine appear more promising than the frequently used PET imaging agent, 8F-FDG, at this time. (*Adapted from* Resnick and Older [4] and Tanagho [5].)

Chance of Cancer on Biopsy

	PSA < 4.0 ng/mL, %	*PSA > 4.0 ng/mL, %*
+DRE findings	6–9	12–32
–DRE findings	10–21	42–72

FIGURE 8-5. Chance of cancer as a function of serum prostate-specific antigen (PSA) level and findings on digital rectal examination (DRE). Men with abnormalities on DRE or PSA elevations—regardless of DRE findings—should be considered for transrectal ultrasound–guided prostatic biopsy because of the higher risk of prostate cancer. With the advent of PSA testing, the majority of prostate cancers (> 60%) are detected in men with PSA elevations but no suspicion of prostate cancer on DRE. Among men with PSA elevations and nonsuspicious rectal examinations, the chance of cancer is 20% to 30% when PSA levels are below 10.0 ng/mL. Thus, most men with PSA elevations do not have cancer (*ie*, the PSA test is not specific among men without prostate cancer). This high false-positive rate among men without cancer has led to a number of approaches to decrease false-positive tests, including PSA density, PSA velocity, age-specific PSA, and percent free PSA. (*Adapted from* Carter and Partin [6].)

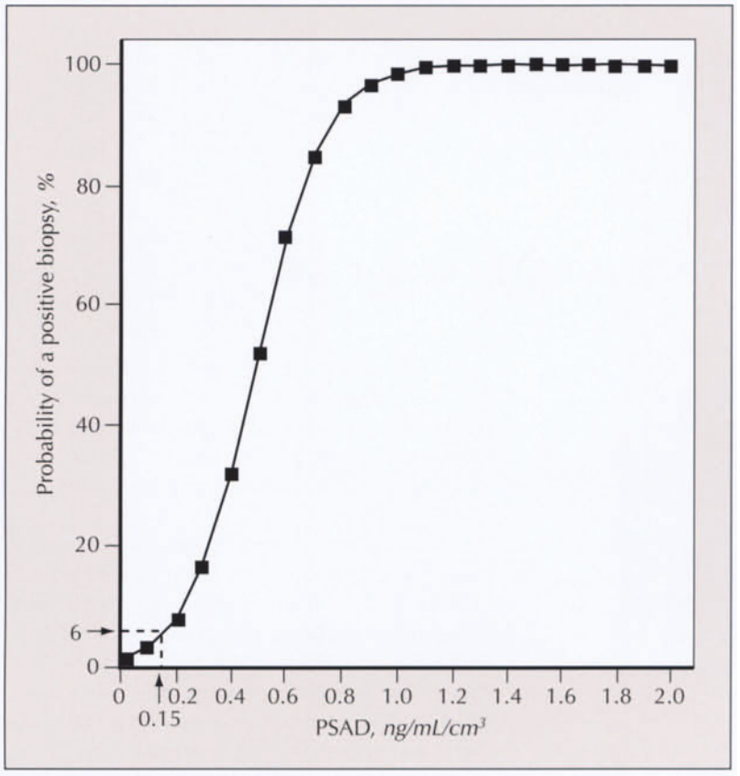


FIGURE 8-6. Probability of a positive prostate biopsy (percent) as a function of prostate-specific antigen (PSA) density (PSAD) among men with PSA levels between 4.0 and 10.0 ng/mL.

More than 80% of men with PSA elevations have levels in the range of 4.0 to 10.0 ng/mL. The most likely reason for the elevation of PSA in these men is prostate enlargement rather than prostate cancer. The PSAD may be useful in assessing the likelihood of a positive biopsy for cancer. PSAD is calculated by dividing the PSA by the ultrasound-determined prostate size. There is a direct relationship between PSAD and the chance of cancer: a PSAD of 0.15 or greater has been proposed as the threshold for recommending prostate biopsy in men with PSA levels between 4.0 and 10.0 ng/mL and no suspicion of cancer on DRE or TRUS. The major determinant of serum PSA in men without prostate cancer is the transition zone epithelium (zone of origin of BPH). Because BPH represents an enlargement of the transition zone, and serum PSA levels are primarily a reflection of transition zone histology in men with BPH, adjusting PSA for transition zone volume may help distinguish between BPH and prostate cancer. Although PSAD is an imperfect predictor of cancer, it is an additional method of risk assessment that is potentially useful for counseling men with intermediate PSA levels (4.0 to 10.0 ng/mL) regarding their need for prostate biopsy. (*Adapted from* Beduschi and Oesterling [7].)

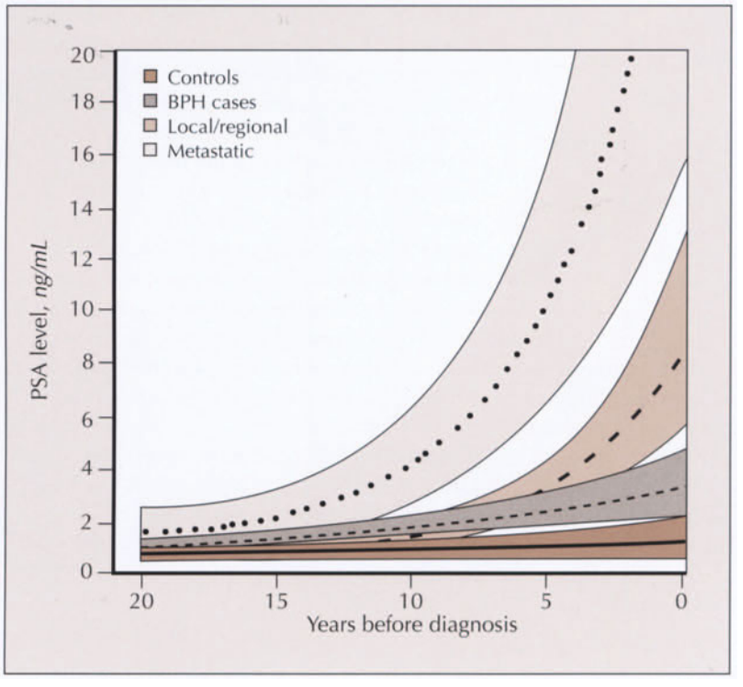


FIGURE 8-7. Average rate of rise of prostate-specific antigen (PSA) levels (95% CI) for men with and without prostate cancer. The rate of rise in PSA (PSA velocity) is greater in men with prostate cancer than men without prostate cancer. Substantial changes or variability in serum PSA (10% to 20%) can occur between measurements in the presence or absence of prostate cancer. The short-term changes in PSA between repeated measurements are primarily caused by physiologic variation. Changes in serum PSA between measurements can be adjusted (corrected) for the elapsed time between the measurements, a concept known as PSA velocity or rate of change in PSA. Evaluation of three repeated PSA measurements to determine PSA velocity can optimize the accuracy for cancer detection. In one study, 5% of men without prostate cancer had a rate of change in PSA of more than 0.75 ng/mL per year, whereas 70% of men with cancer had a rate of change in PSA more than 0.75 ng/mL per year. The cancer detection rate in a large prospective screening study was 47% among men with a PSA velocity more than 0.75 ng/mL per year, compared with 11% among men with a PSA velocity less than 0.75 ng/mL per year. BPH—benign prostatic hyperplasia. (*Adapted from* Carter *et al.* [8].)

"Normal" PSA Ranges (ng/mL) Among White and Black Men in the United States

Age Decade	Based on 95% Specificity*		Based on 95% Sensitivity†	
	White [9]	Black [10]	White [10]	Black [10]
40	0–2.5	0–2.4	0–2.5	0–2.0
50	0–3.5	0–6.5	0–3.5	0–4.0
60	0–4.5	0–11.3	0–3.5	0–4.5
70	0–6.5	0–12.5	0–3.5	0–5.5

*Upper limit of normal PSA determined from 95% percentile of PSA among men without prostate cancer.
†Upper limit of normal PSA required to maintain 95% sensitivity for cancer detection.

FIGURE 8-8. Age- and race-specific prostate-specific antigen (PSA) levels. The 95th percentile of PSA levels seen in men without prostate cancer (95% specificity) and the PSA range required to maintain the detection of 95% of prostate cancers (95% sensitivity) have been used to establish "normal" age-specific reference ranges among black and white men. PSA increases with age, primarily because of increases in prostate size, and age-adjustment of PSA are ways of accounting for this size increase with age. It has been suggested that use of an age-adjusted PSA rather than a single PSA cutoff for all ages may lead to increased cancer detection in younger men more likely to benefit from treatment and minimize unnecessary evaluations in older men who are less likely to benefit from treatment. It has been shown that PSA levels are higher in black men without prostate cancer than in white men without prostate cancer of the same age. It has not definitely been shown, however, that use of age- or race-specific reference ranges has an advantage in detecting curable cancer over the use of a single cut-point of 4.0 ng/mL. Currently, the data suggest that a cut-point of 4.0 ng/mL—using the Tandem assay (Hybritech, San Diego, CA)—is an effective threshold for maximizing prostate cancer detection and minimizing unnecessary biopsies in men between the ages of 50 and 70 years. The optimal PSA threshold, *ie*, the cutoff that will result in detection of clinically significant cancers in those men who are most likely to benefit from treatment, is not known. For younger men, a greater index of suspicion is warranted at PSA levels below 4.0 ng/mL because the relative risk of cancer is increased even at PSA levels between 2.0 and 4.0 ng/mL: these men have the most to gain from early diagnosis and treatment of prostate cancer. A greater suspicion of prostate cancer at lower PSA levels is especially important in the setting of known risk factors of family history and black race. The use of higher PSA thresholds among older men, who are less likely to benefit from prostate cancer treatment, should take into consideration the overall health and life expectancy of the individual.

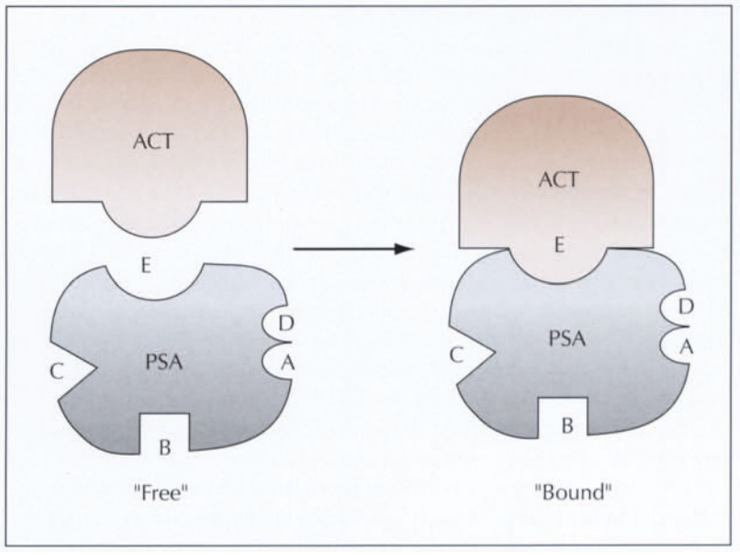


FIGURE 8-9. Free and total prostate-specific antigen (PSA). Little controversy exists regarding the clinical utility of serum PSA measurements for detection, staging, and monitoring of men with prostate cancer. However, total serum PSA levels between 4.0 and 10.0 ng/mL (the diagnostic "gray zone") have led physicians to perform biopsies of nearly all their patients with prostate cancer in an attempt to identify the 25% who ultimately will harbor malignancy and potentially require therapy. The goal of any modification to the total PSA test is to maintain its sensitivity for cancer detection as close to 100% as possible while improving specificity. The recently introduced modification to the standard total PSA test, percent free PSA, may provide the best means of distinguishing prostate cancer from benign prostatic conditions within this diagnostic gray zone. The free form of PSA represents an enzymatically inactive nonprotein-bound form of PSA that ranges anywhere from 5% to 50% of total measured PSA. α1-Antichymotrypsin (ACT) and α2-macroglobulin (α2M) are the two major protease inhibitors that complex with active PSA in the blood, thereby inactivating PSA. ACT covalently bonds to PSA, whereas α2M acts through steric interference. PSA-ACT can be found in concentrations ranging from 50% to 90% of total measured PSA. Prostate cancer tends to produce higher levels of active PA\SA than BPH, which complexes with ACT or α2M in the serum. Percent-free PSA has been shown to assist in distinguishing prostate cancer from other benign prostatic conditions in men who have serum PSA levels between 4.0 and 10.0 ng/mL. Data from a multi-institutional prospective trial have demonstrated that using the Hybritech (Beckman-Coulter, Inc., Chaska, NY) percent-free PSA assay and a cut-off of 25% free PSA, 95% of prostate cancers are still detected and 20% of unnecessary biopsies are avoided. Physicians should be aware that different PSA assays perform differently and they should discuss with their reference laboratories the recommended criteria for sample collection, storage conditions, and shipping, as well as the recommended cut-offs of and the clinical trials supporting the data for the assay being used. Percent-free PSA may improve our diagnostic armamentarium for decision-making in men who have normal digital rectal examination findings but elevated serum total PSA. The best use of this assay at present is in determining the need for repeat biopsies among men who fit these criteria and have had at least one previous negative biopsy. (*Adapted from* Partin [11].)

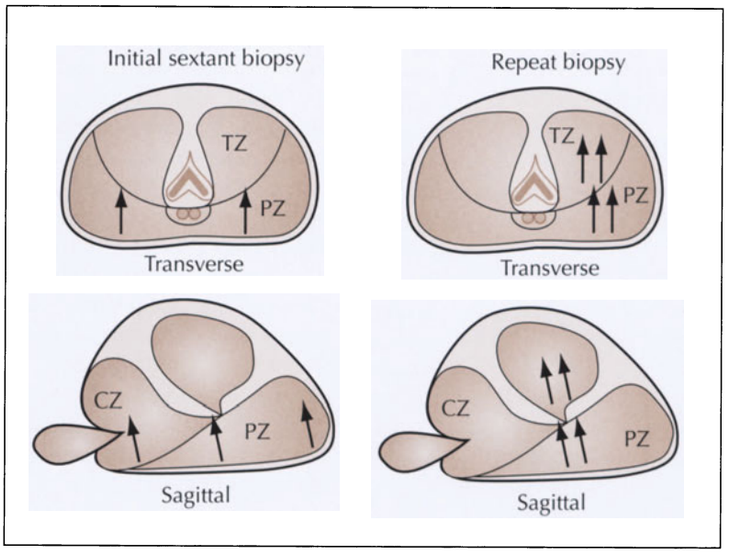


FIGURE 8-10. Use of transrectal ultrasound for diagnosis of prostate cancer. The diagnosis of prostate cancer is made solely through histologic examination of prostate tissue obtained through biopsy techniques.

Recently, advances in the knowledge of prostate-specific antigen and ultrasound technology have made it easier to identify men who have prostate cancer. Since the 1930s, prostate biopsies have become routine procedure, first with digitally guided transperineal biopsies and then by fine-needle aspirations. The use of a transrectal ultrasound became available in the 1980s, allowing better imaging and transrectal ultrasound biopsy approaches (TRUS). Systematic evaluation of the prostate gland using sextant biopsies was described and popularized by Stamey [12] from Stanford University and has become the standard approach. To perform transrectal ultrasound–guided biopsies of the prostate, it is essential to understand the zonal anatomy of the prostate (transition and peripheral zones). A preliminary transrectal diagnostic ultrasound scan should be performed to allow calculation of prostate size and indicate the presence of abnormalities that may guide additional directed biopsies following the sextant biopsy procedure. Biopsy specimens of all palpable lesions and specific lesions suspicious on ultrasound should be obtained as well as the collection of guided sextant biopsy material. The diagnostic yield and increased pain of transition zone biopsies does not support the routine use of this technique on initial biopsy of the prostate. They are often recommended when a patient has had a previous histologically negative biopsy but has a persistent elevation of PSA (4.0 to 10.0 ng/mL). (*Adapted from* Terris et al. [13].)

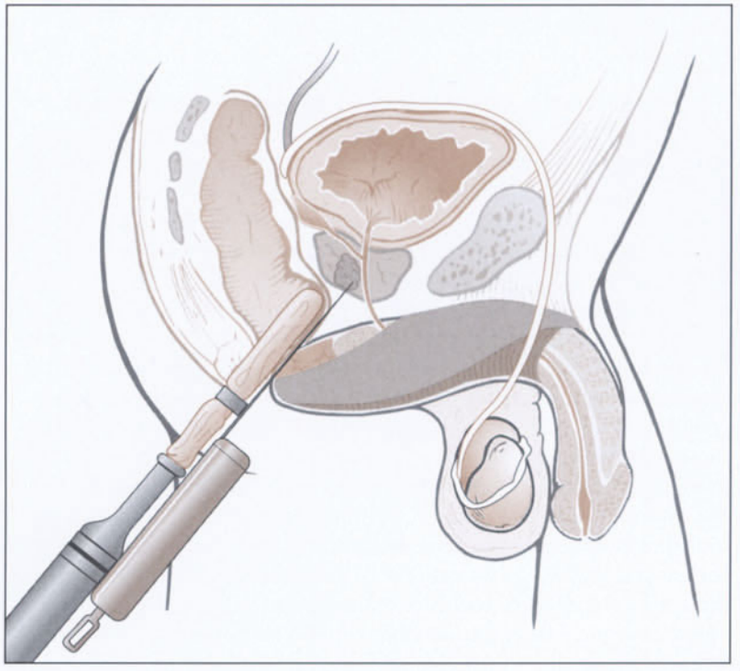


FIGURE 8-11. Transrectal ultrasound (TRUS) for early detection. When prostate cancer is suspected because of an elevated prostate-specific antigen (PSA) level or an abnormal digital rectal examination, histologic confirmation of adenocarcinoma of the prostate is essential before treatment decisions are made. The volume, location, pretreatment PSA, and grade of tumor are the most critical issues involved in the decision to undergo definitive therapy, the choice of type of definitive therapy, and the urgency with which therapy should be delivered. Since TRUS-guided biopsy was introduced, a number of different biopsy techniques have been used. The currently recommended method for biopsy of the prostate from the transrectal approach is to perform a sextant biopsy of palpable lesions. Various parameters can be determined from the TRUS imaging: 1) the volume of the prostate (essential in calculating PSA density); 2) the degree of differentiation between the peripheral and central zones of the prostate; 3) the presence of abnormalities along the posterior border of the prostatic capsule and the lateral edges of the prostate suggestive of extensive capsular penetration; 4) asymmetry in the size and shape of the prostate gland; and 5) echo texture patterns within the prostatic tissue itself. Many prostate cancers demonstrate a hypoechoic feature when analyzed with TRUS. Unfortunately, because nearly 75% of prostate cancers originate within the peripheral zone of the prostate, which itself is hypoechoic in nature, use of this technique is significantly limited. The use of color Doppler TRUS coupled with enhancing agents for identifying vascular structures has increased the ability to characterize inflammatory, normal, and cancerous tissue within the prostate. (*Adapted from* Kirby *et al.* [14].)

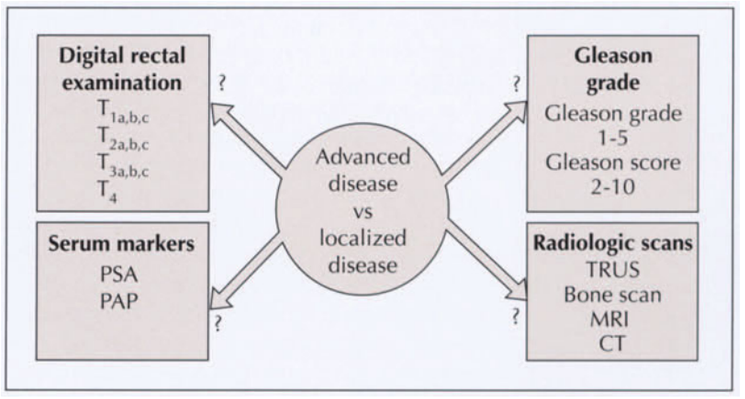


FIGURE 8-12. General concepts in the staging of prostate cancer. Management of organ-confined prostate cancer is based on accurate and interpretable prognostic information. Clinical staging of prostate cancer is one parameter that is necessary to assess the patient's chances of having organ-confined disease, locally advanced cancer, or metastases. The other prognostic parameters include histologic tumor grade (Gleason score), serum markers such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), and other radiologic studies such as transrectal ultrasound (TRUS), bone scan, MRI, and CT. In organ-confined (curable) prostate adenocarcinoma, the treatment options often are highly individualized and are influenced by experience and opinions of the physician, as well as the knowledge and concerns of the patient. (*Adapted from* Partin [15–17].)

Prostate Cancer Clinical Staging Systems

TNM Stage	*Description*	*Whitmore-Jewett Stage*	*Description*
T1a	Nonpalpable, with ≤ 5% of resected tissue with cancer, not high grade	A1	Same as TNM
T1b	Nonpalpable, with > 5% of resected tissue with cancer and/or high grade	A2	Same as TNM
T1c	Tumor identified by needle biopsy (*eg*, because of elevated PSA)		
T2a	Palpable, half of one lobe or less	B1N	Palpable, < one lobe surrounded by normal tissue
		B1	Palpable, < one lobe
T2b	Palpable, > half of one lobe but not both lobes	B1	Palpable, < one lobe
		B2	Palpable, one entire lobe or more
T2c	Palpable, involves both lobes	B2	Palpable, one entire lobe or more
T3a	Palpable, unilateral capsular penetration	C1	Palpable, outside capsule, not into seminal vesicles
T3b	Bilateral capsular penetration	C1	Same as TNM
T3c	Tumor invades seminal vesicles	C2	Same as TNM
T4	Tumor invades other structures (*eg*, bladder neck, levator muscle, or sphincter)	C2	Same as TNM

FIGURE 8-13. Prostate cancer clinical staging systems. Clinical staging for prostate cancer requires making an accurate assessment of the extent of disease spread, which can be determined through digital rectal examination (DRE), serum tumor markers, histologic grade, and various imaging modalities. The determination of the local extent of disease (T stage) is performed primarily through DRE. This table presents a description of the DRE findings for various T stages, and also characterizes clinical staging of prostate cancer in an older, ABCD (Whitmore-Jewett) classification system. Pathologic stage, a more accurate representation of the extent of disease, can be described only following histologic examination of the surgical material removed at the time of radical prostatectomy. Although pathologic stage is more useful than is clinical staging in the prediction of prognosis, it cannot be determined with presurgical information. Thus, this currently accepted tumor-node-metastasis (TNM) clinical staging system for prostate cancer has been used to subcategorize patients based on their likelihood of disease spread prior to definitive therapy. (*Adapted from* Carter and Partin [6].)

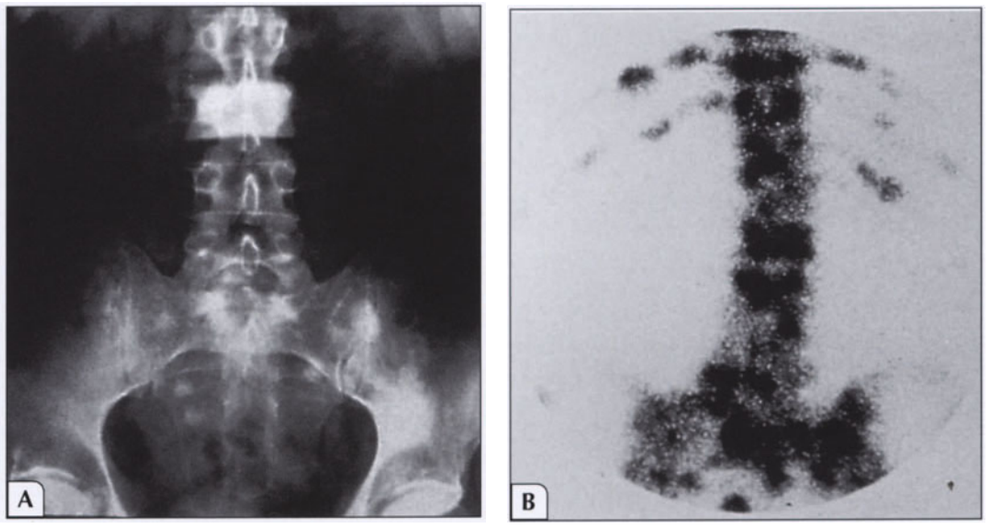


FIGURE 8-14. Bone scan for staging of prostate cancer. **A**, Plain film. **B**, Bone scan. Accurate prediction of extraprostatic disease spread before therapeutic decision making is fundamental to prediction of prognosis and staging. The radionuclide bone scan, which has high sensitivity and poor specificity, is widely used for detecting distant bony metastases. In men considered for curative therapy with prostatectomy or radiation therapy, who have a Gleason score of less than 8, a T1 or T2 lesion, and a prostate-specific antigen (PSA) less than 10 ng/mL, a bone scan is not necessary as part of the initial evaluation because the likelihood of bone metastases are exceedingly small. In men with high-grade cancer, PSA levels exceeding 10 ng/mL, bone symptoms, T3 or T4 tumors, or Gleason score of 8 or more, a bone scan can help determine the existence of osseous metastases. (*From* ICI Pharmaceutical [16]; with permission.)

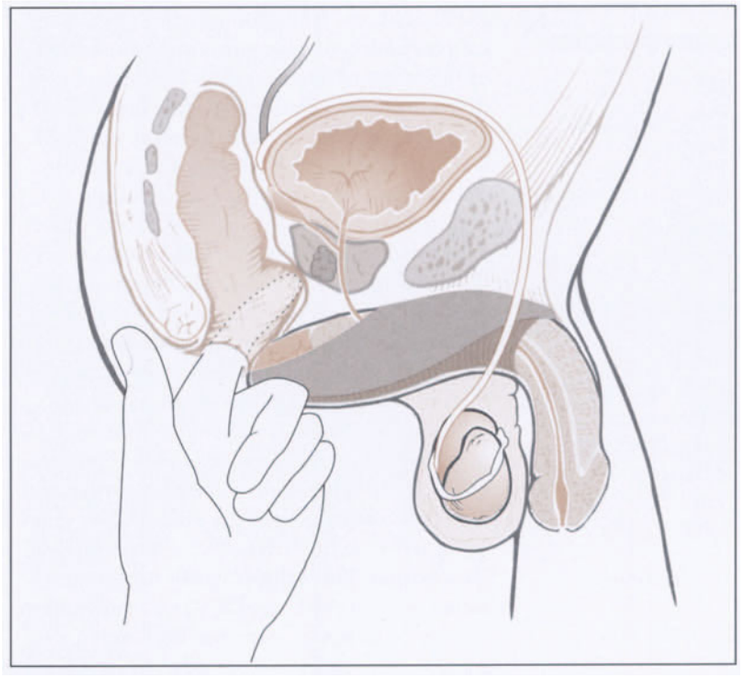


FIGURE 8-15. Digital rectal examination (DRE). DRE was the "gold standard" for detection and determination of prognosis of prostate cancer long before the development of modern urologic practice. Although DRE as part of a routine physical examination is a common practice for primary care providers, its role as a screening tool for prostate cancer is poor. The reported predictive value for DRE in asymptomatic men is 6% to 33% and may be higher for urologists. The poor predictive value is due to cancers developing in inaccessible sites of the gland and cancers of small volume. Furthermore, screening for prostate cancer with DRE or DRE and prostate-specific antigen (PSA) has not yet proven to reduce prostate cancer mortality. The report of the US Preventive Services Task Force has recommended that patients be given the necessary information regarding the risks and benefits of screening. When tumors are detected, large tumor volume and the presence of palpable disease outside the prostate are poor prognostic signs. DRE has a sensitivity of 52% and a specificity of 81% for prediction of organ-confirmed status. Prediction of organ-confined disease can be improved by incorporating the PSA level and the Gleason score in a nomogram (see Fig. 8-20). (*Adapted from* Kirby *et al.* [14].)

Serum Markers as Predictors of Prognosis

Prostate-specific, *not* prostate cancer–specific
Produced by prostate epithelial cells (luminal)
Increased serum PSA indicates prostatic disease
Interpretation of PSA elevation limited
Not normally accurate for staging or prognosis prediction

FIGURE 8-16. Serum prostate-specific antigen (PSA) for clinical staging of prostate cancer. PSA is a serine protease made exclusively by prostatic luminal epithelial cells, both normal and cancerous. PSA has also been detected in breast tissue and amniotic fluid. The major role of PSA is to liquefy the seminal coagulum. In certain prostatic disease states, PSA can "leak" into the intravascular spaces and its presence can be detected in the serum. The use of PSA as a prognostic marker has been limited secondary to the fact that it is produced in higher-than-normal amounts by the prostates of men with benign prostatic hyperplasia (BPH) as well as by men with prostatic adenocarcinoma. Serum PSA levels in men with prostate cancer ultimately depend on prostate volume, tumor volume, and the degree of tumor differentiation. Tumors of higher grade often are associated with levels of PSA production that are lower than expected. In general, a pretreatment PSA level greater than 100 ng/mL represents advanced disease and is associated with a poor prognosis. By contrast, serum PSA levels lower than normal (< 4.0 ng/mL) are often associated with less aggressive tumors. Most men with prostate cancer (> 75%) present with serum PSA levels between these two extreme values. Within this range, the PSA level alone, although directly correlating with disease extent, is by no means an accurate method for staging prostate cancer. The contribution of BPH to overall serum PSA has been estimated to be from 0.15 to 0.3 ng/mL per gram of BPH tissue. An accurate assessment of the BPH contribution to the overall serum PSA level currently is not possible for an individual patient because 1) the epithelial component of BPH is the major source of PSA, 2) BPH tissue contains variable amounts of epithelium and stroma, and 3) no minimally or noninvasive methods currently are available to distinguish between epithelium and stroma within BPH tissue. Another confounding factor demonstrated by Partin [15] suggests that men with prostate cancer presenting at a more advanced stage and higher grade have higher volume tumors, which produce less PSA per gram of epithelial cells. (*Adapted from* Partin [15].)

Prediction of Pathologic Stage by Imaging Techniques

Technique	*Sensitivity, %*	*Specificity, %*
Extracapsular penetration		
TRUS	(50–89)	(50–94)
CT	(35–75)	(60–73)
MRI	(35–77)	(57–88)
Seminal vesicle involvement		
TRUS	(20–100)	(85–100)
CT	(33–36)	(60–96)
MRI	(50–83)	(88–97)
Pelvic lymph nodal involvement		
CT	(0–100)	(86–96)
MRI	(44–69)	(95–100)

FIGURE 8-17. Prediction of pathologic stage by imaging techniques. Imaging techniques, including transrectal ultrasound (TRUS), CT, MRI (both body and endorectal), and PET have proved to be disappointing as pretherapy predictors of pathologic stage. TRUS and MRI are useful mainly in determining the local extent of prostate cancer. Pelvic imaging with either CT or MRI for the detection of lymph node metastasis has not been routinely useful secondary to low sensitivity. (*Adapted from* Gishman and deVere White [18].)

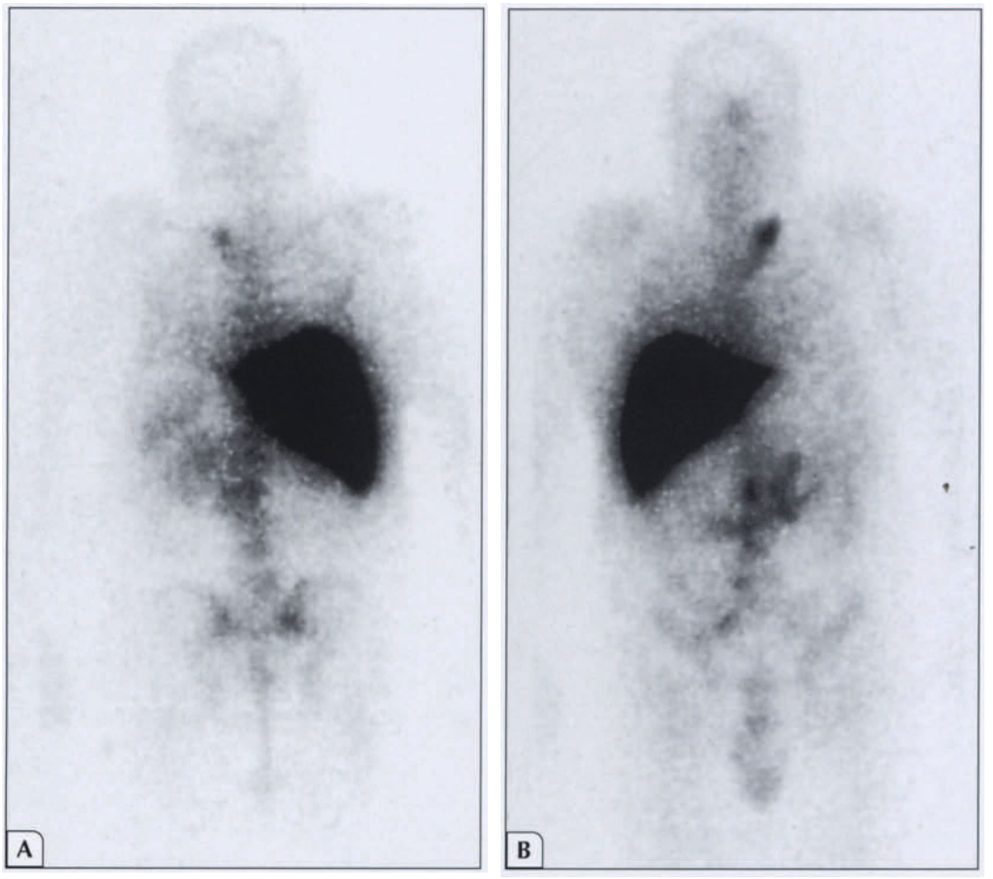


FIGURE 8-18. Immunoscintigraphy (ProstaScint; Cytogen Corp., Princeton, NJ). **A**, Immediate posterior day-1 scan. **B**, Delayed anterior day-4 scan. These ProctaScint images demonstrate abdominal soft tissue prostate cancer metastasis. ProctaScint recently was approved as a diagnostic imaging agent for patients with newly diagnosed, clinically localized prostate cancer who are at high risk for pelvic and abdominal lymph node metastases. This radiolabeled monoclonal antibody targets a membrane-associated antigen on prostate cells (prostate-specific membrane antigen [PSMA]). PSMA is more highly expressed in malignant than in nonmalignant prostate cells. PSMA also appears to be more highly expressed in metastatic soft tissue lesions than in primary prostate cancers. Preliminary data suggest that immunoscintigraphy with ProctaScint might be used to identify possible sites of disease metastases both before therapy in patients with relatively high risk for nodal involvement and in patients with biochemical evidence (detectable PSA levels) of recurrent or residual disease following prostatectomy. Preliminary data presented to the Food and Drug Administration demonstrated that ProctaScint provided a sensitivity of 62% and a specificity of 72%. In the same group of patients, CT was less accurate in detecting soft tissue metastases. The ProctaScint scan has been useful in documenting the presence of soft tissue metastases beyond the pelvis that are not amenable to adjuvant pelvic radiation therapy. Recent data also have demonstrated that modifications to radiation fields in the presence of pelvic recurrence based on the findings of the ProctaScint scan has provided some improved benefit. Preliminary data have demonstrated that use of clinical, pathologic, and ProctaScint imaging information can improve the prediction of local recurrence versus distant metastases and help in rational decision making with respect to adjuvant therapy for recurrent or occult metastatic prostate cancer. (*Courtesy of* M. Haseman, MD.)

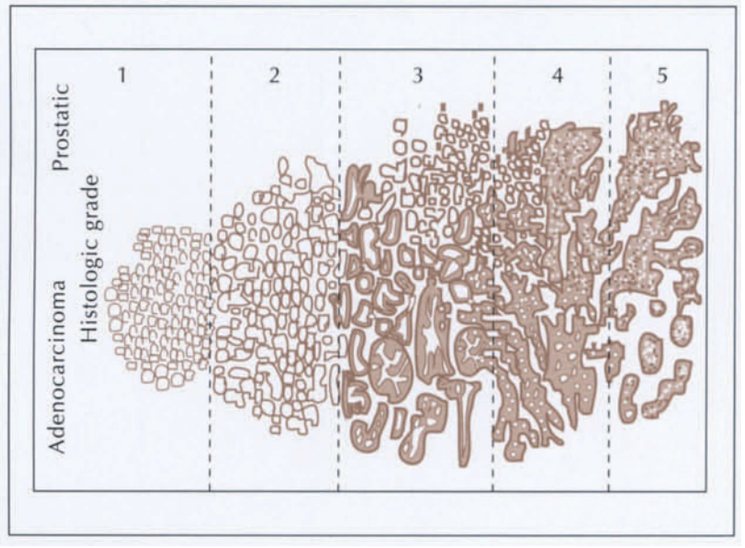


FIGURE 8-19. Gleason grading system. In the 1960s, as part of a pathologic analysis of prostate cancer specimens collected during the Veterans Administration Cooperative Urologic Research Group studies, Gleason introduced a prostate cancer grading system based on low-magnification microscopic assessment of glandular patterns of prostate tissue. A Gleason grade from 1 to 5 is assigned to the primary tumor pattern and also to the secondary tumor pattern based on the degree of disorder of the tissue. A Gleason score is obtained by combining these numbers. Thus, a patient with a diagnosis of prostate cancer may have a Gleason score of between 2 and 10. For example, a patient with a large amount of grade 2 tumor and a small amount of grade 3 tumor will have a Gleason score of 2 + 3 = 5, whereas a patient with a large amount of grade 4 tumor and a small amount of grade 3 tumor will have a Gleason score of 4 + 3 = 7. When only one tumor pattern is evident, the grade is doubled to give the score. Based on current practice, the correlation between Gleason score and prognosis is accurate for specific populations. Gleason scores from sextant biopsies with Gleason scores from paired prostatectomy samples in about 45% to 50% of the cases. In the remaining paired samples, biopsy Gleason scores tended to undergrade the final pathology (increasing from well-differentiated scores to moderate differentiation). Gleason score from biopsy, although undergrading compared with prostatectomy scores, remains an important prognostic factor. More recent studies from Stamey *et al.* [19] and Pan *et al.* [20] strongly suggest that even a minute component of pattern 4/5 is associated with PSA failures. Men with Gleason scores on the outer edges of the range (*ie*, 2 to 4 or 8 to 10), who constitute only 20% of the total population, demonstrate a marked correlation between Gleason score and prognosis. Unfortunately, most men (> 75%) demonstrate Gleason scores of 5 to 7. For this group of men, the correlation between grade and prognosis is very poor. We conclude that Gleason score alone has prognostic value; however, for men with Gleason scores of 5 to 7, it has provided little or poor prognostic information. Improvements in our methods for histologic grading system are desperately needed [19,20]. (*Adapted from* Gleason [21].)

Nomogram for Prediction of Final Pathologic Stage

	PSA 0.0–4.0 ng/mL Clinical Stage							PSA 4.1–10.0 ng/mL Clinical Stage						
Gleason Score	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3a**	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3a**
Organ-confined Disease														
2–4	90	80	89	81	72	77	—	84	70	83	71	61	66	43
5	82	66	81	68	57	62	40	72	53	71	55	43	49	27
6	78	61	78	64	52	57	35	67	47	67	51	38	43	23
7	—	43	63	47	34	38	19	49	29	49	33	22	25	11
8–10	—	31	52	36	24	27	—	35	18	37	23	14	15	6
Established Capsular Penetration														
2–4	9	19	10	18	25	21	—	14	27	15	26	35	29	44
5	17	32	18	30	40	34	51	25	42	27	41	50	43	57
6	19	35	21	34	43	37	53	27	44	30	44	52	46	57
7	—	44	31	45	51	45	52	36	48	40	52	54	48	48
8–10	—	43	34	47	48	42	—	34	42	40	49	46	40	34
Seminal Vesicle Involvement														
2–4	0	1	1	1	2	2	—	1	2	1	2	4	5	10
5	1	2	1	2	3	3	7	2	3	2	3	5	6	12
6	1	2	1	2	3	4	7	2	3	2	3	5	6	11
7	—	6	4	6	10	12	19	6	9	8	10	15	18	26
8–10	—	11	9	12	17	21	—	10	15	15	19	24	28	35
Lymph Node Involvement														
2–4	0	0	0	0	0	0	—	0	1	0	0	1	1	1
5	0	1	0	0	1	1	2	1	2	0	1	2	2	3
6	1	2	0	1	2	2	5	3	5	1	2	4	4	9
7	—	6	1	2	5	5	9	8	12	3	4	9	9	15
8–10	—	14	4	5	10	10	—	18	23	8	9	16	17	24

(Table continued on next page)

FIGURE 8-20. Nomograms to predict pathologic stage. The prognostic value of any clinical marker used to predict pathologic stage is limited for the individual patient with prostate cancer when used alone. Staging accuracy for prostate cancer can be significantly enhanced through combinations of these markers. Partin *et al.* [22], in a multi-institutional study combining more than 4000 patients from The Johns Hopkins Medical Institutions, the Baylor College of Medicine, and the University of Michigan, combined clinical staging (tumor-node-metastasis stage), serum prostate-specific antigen (PSA) level, and Gleason histologic score from prostate biopsy specimens to develop nomograms to allow patients and their treating physicians to assess the probability of pathologic stage from preclinical variables. The numbers within the nomograms represent the percent probability of having a given pathologic stage based on logistic regression analyses for all three variables combined (95% CIs were provided within the original publication). This information has been very useful in counseling men with newly diagnosed prostate cancer about treatment alternatives and the probability of complete eradication of tumor. For example, a man with a serum PSA level of 3.0 ng/mL who has a clinical stage T2a cancer with a Gleason score of 5 has a 68% chance of having organ-confined disease, whereas a man with a serum PSA of 15 ng/mL with a clinical stage T2a cancer and a Gleason score of 8 has only a 14% chance of having organ-confined disease. This type of nomogram may help patients and physicians make more informed decisions based on the probability of a pathologic stage. An individual's risk tolerance and the values placed on various potential outcomes will then be used to guide treatment decisions. Use of these nomograms may aid in rational selection of patients to undergo definitive therapy for clinically localized prostate cancer with the hope of improving the percentage of cancers found to be organ-confined and, potentially, cured with definitive therapy alone. (*Adapted from* Partin *et al.* [22] and TAP Pharmaceuticals [23].)

(*Continued on next page*)

Nomogram for Prediction of Final Pathologic Stage (Continued)

	PSA 10.1–20.0 ng/mL Clinical Stage							PSA >20.0 ng/mL Clinical Stage						
Gleason Score	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3a**	**T1a**	**T1b**	**T1c**	**T2a**	**T2b**	**T2c**	**T3a**
Organ-confined Disease														
2–4	76	58	75	60	48	53	—	—	38	58	41	29	—	—
5	61	40	60	43	32	36	18	—	23	40	26	17	19	8
6	—	33	55	38	26	31	14	—	17	35	22	13	15	6
7	33	17	35	22	13	15	6	—	—	18	10	5	6	2
8–10	—	9	23	14	7	8	3	—	3	10	5	3	3	1
Established Capsular Penetration														
2–4	20	36	22	35	43	37	—	—	47	34	48	52	—	—
5	33	50	35	50	57	51	59	—	57	48	60	61	55	54
6	—	49	38	52	57	50	54	—	51	49	60	57	51	46
7	38	46	45	55	51	45	40	—	—	46	51	43	37	2
8–10	—	33	40	46	38	33	26	—	24	34	37	28	23	17
Seminal Vesicle Involvement														
2–4	2	4	2	4	7	8	—	—	9	7	10	14	—	—
5	3	5	3	5	8	9	15	—	10	9	11	15	19	26
6	—	4	4	5	7	9	14	—	8	8	10	13	17	21
7	8	11	12	14	18	22	28	—	—	22	24	27	32	36
8–10	—	15	20	22	25	30	34	—	20	31	33	33	38	40
Lymph Node Involvement														
2–4	0	2	0	1	1	1	—	—	4	1	1	3	—	—
5	3	5	1	2	4	4	7	—	10	3	3	7	7	11
6	—	13	3	4	10	10	18	—	23	7	8	16	17	26
7	18	24	8	9	17	18	26	—	—	14	14	25	25	32
8–10	—	40	16	17	29	29	37	—	51	24	24	36	35	42

FIGURE 8-20. *(Continued)* Nomograms to predict pathologic stage.

A. Nomogram to Predict PSA Failure after Radical Prostatectomy

Preoperative PSA	*Points*
0.1	0
0.5	35
1.0	50
5.0	81
100	92
	100

Prostate Capsule Invasion	
None	0
Invasive capsule	30
Focal	49
Established	55

Lymph Node	
Negative	0
Positive	26

Σ Points from Preoperative PSA, GS, PCI, SM, LN, SVI	
84-Month Recurrence-free Probability, %	*Σ Points*
1	245
10	225
30	205
50	190
70	172
80	156
90	135
95	115
98	90
99	70

Gleason Score	*Points*
3	0
4	0
5	0
6	4
7	28
9	56
10	71

Surgical Margin	
Negative	0
Positive	32

Seminal Vesicle Invasion	
No	0
Yes	24

FIGURE 8-21. Nomograms to predict failure after prostatectomy (**A**) and primary radiotherapy (**B**).

A, The ability to predict prostate-specific antigen (PSA) failures after prostatectomy helps identify men at high risk for surgical failure who may benefit from additional adjuvant therapy. This nomogram was developed at the Baylor School of Medicine and validated in 2465 patients from multiple institutions.

(*Continued on next page*)

B. Nomogram to Predict PSA Failure after Radiation Therapy

Pretreatment PSA	Gleason Score	T1c	T2a	T2b	T2c
0–4.0	2–4	3 (1–5)	4 (2–7)	5 (3–9)	6 (3–9)
	5	7 (4–10)	8 (5–12)	11 (7–16)	12 (7–17)
	6	10 (6–14)	12 (8–17)	16 (10–23)	17 (11–24)
	7	14 (9–20)	18 (11–25)	23 (15–34)	25 (17–35)
	8–10	29 (17–46)	36 (21–55)	45 (27–68)	48 (29–69)
4.1–10.0	2–4	4 (2–6)	5 (2–8)	6 (3–10)	7 (3–11)
	5	8 (5–11)	10 (6–14)	13 (8–18)	14 (9–20)
	6	11 (7–15)	14 (9–19)	18 (12–26)	20 (13–27)
	7	16 (11–23)	20 (13–28)	26 (17–37)	28 (19–39)
	8–10	33 (20–50)	40 (24–59)	50 (31–72)	52 (33–74)
10.1–20.0	2–4	4 (2–8)	5 (3–10)	7 (4–13)	8 (4–14)
	5	9 (6–14)	12 (7–17)	16 (10–22)	17 (11–24)
	6	14 (9–19)	17 (11–24)	22 (15–31)	24 (17–33)
	7	20 (13–27)	25 (16–34)	32 (22–44)	34 (24–46)
	8–10	39 (25–57)	47 (30–67)	58 (38–79)	61 (40–81)
20.1–50.0	2–4	7 (3–14)	9 (4–18)	12 (6–23)	13 (7–24)
	5	16 (10–24)	20 (13–30)	26 (16–37)	27 (17–39)
	6	23 (15–32)	28 (20–39)	36 (25–49)	38 (27–51)
	7	32 (23–42)	39 (28–51)	49 (36–64)	51 (38–66)
	8–10	58 (41–76)	67 (49–85)	78 (58–93)	80 (62–94)

Numbers indicate percent PSA failure at 2 years; numbers in parentheses indicate 95% CI.

FIGURE 8-21. ***(Continued)*** **B**, Similarly, the ability to predict PSA failures after primary radiation therapy would help identify men at high risk for failure and who may benefit from additional adjuvant therapy. This nomogram is derived from 763 patients treated at the Joint Center for Radiation Therapy in Boston. It also provides data on risk for relapse at 2 years and has not yet been subjected to a validation study. GS—Gleason score; LN— lymph node; PCI—prostate capsule invasion; SM—surgical margin; SVI—seminal vesicle invasion. (**A** *adapted from* Graefen *et al.* [24]; **B** *adapted from* D'Amico *et al.* [25].)

PATHOLOGIC CONSIDERATIONS

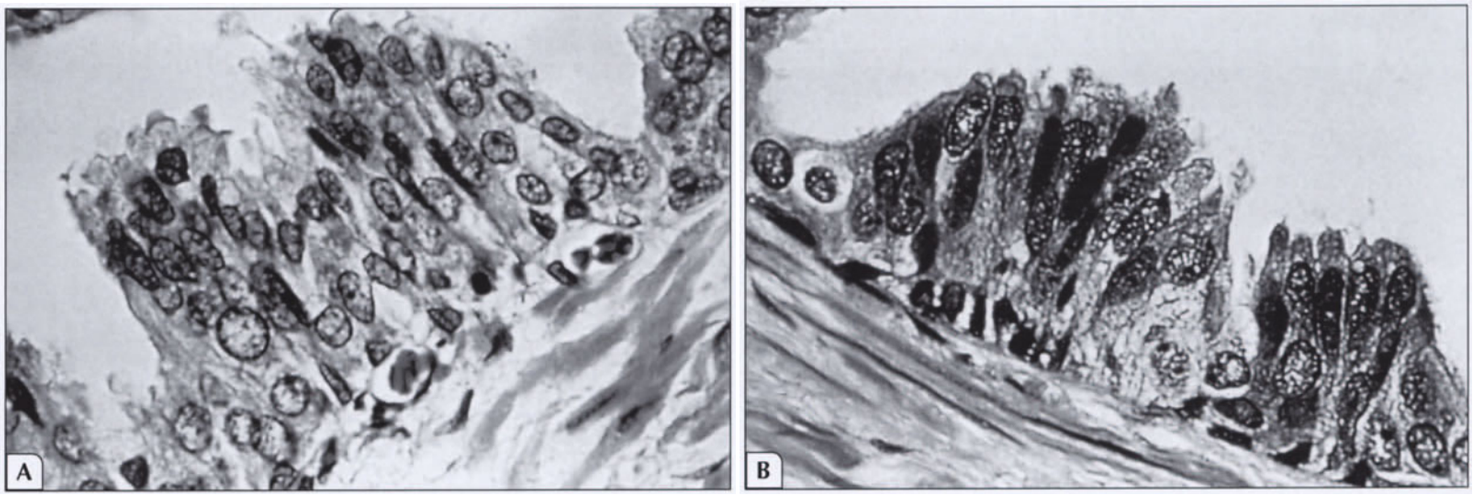
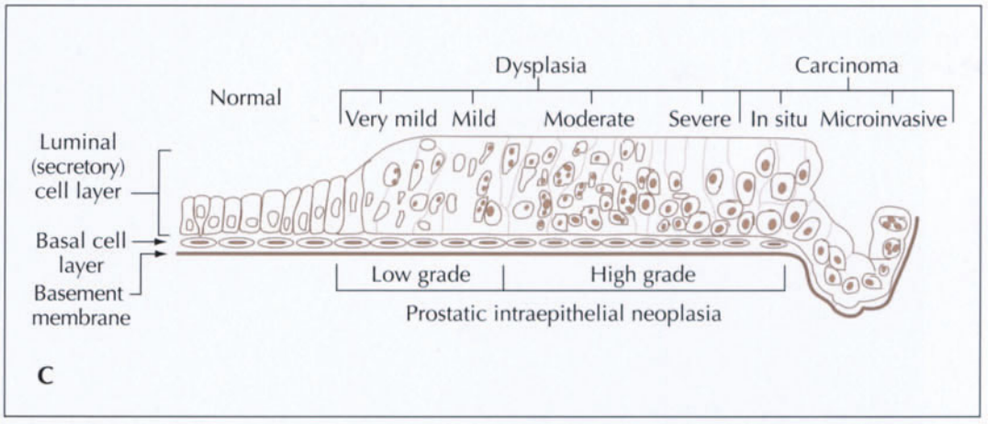


FIGURE 8-22. Prostatic intraepithelial neoplasia. The precursor lesion to invasive carcinoma of the prostate is high-grade prostatic intraepithelial neoplasia (PIN). Prostatic intraepithelial neoplasia is an architecturally benign prostate gland lined with cytologically atypical cells. This pathologic entity, first described by Bostwick and Brawer in 1987, replaced previously described pathologic lesions of the prostate such as atypical and intraductal dysplasia. Originally, PIN was divided into three categories: PIN-1, mild dysplasia (**A**); PIN-2, moderate dysplasia; and PIN-3, severe dysplasia (**B**).

(*Continued on next page*)



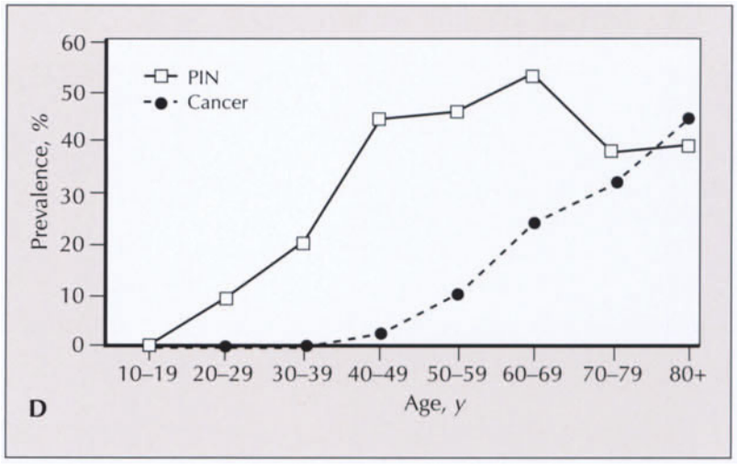


FIGURE 8-22. ***(Continued)*** Currently, the only pathologic entity of clinical significance is believed to be PIN-3 or high-grade PIN. Pathologic studies have demonstrated that the reproducibility of low-grade PIN as a diagnosis is limited. In addition, when low-grade PIN (PIN-1 or -2) is diagnosed via needle biopsy, men were found to be at no greater risk of having prostatic carcinoma on repeat biopsies.

Panels A and *B* demonstrate the histologic difference between low-grade PIN and high-grade PIN. **C**, The histologic continuum proposed by Bostwick and Brawer in which normal columnar prostatic epithelium can differentiate into the various forms of prostatic intraepithelial neoplasia and on into carcinoma in situ and invasive cancer. High-grade PIN shares several histologic characteristics with invasive prostate cancer: 1) marked variation in nuclear size and shape; 2) increased heterogeneity in chromatin texture patterns; 3) increased number and variability of nucleoli; and 4) a decrease in the architectural order with which cells are arranged on the basement membrane. In addition, several phenotypic similarities have been noted between high-grade PIN and carcinoma of the prostate. Immunohistochemical studies have demonstrated a decrease in PSA, prostatic acid phosphatase (PAP), and other markers of prostatic neoplasia, as well as progressive increases in various tissue factors such as type IV collagenase, acidic mucin, and other markers of invasive prostate cancer. **D**, The parallel increase in histologic diagnosis of PIN and prostate cancer from autopsy series. Current clinical recommendations dictate repeat prostatic biopsies when a diagnosis of high-grade PIN has been made. When high-grade PIN is found on needle biopsy, there is a 30% to 50% risk of finding carcinoma on subsequent biopsies. PIN by itself does not, however, give rise to elevated serum PSA levels. When PIN has been diagnosed, repeat biopsies should include wide sampling of the prostate in addition to the area in which PIN was found. (**C** *adapted from* Bostwick [26].)

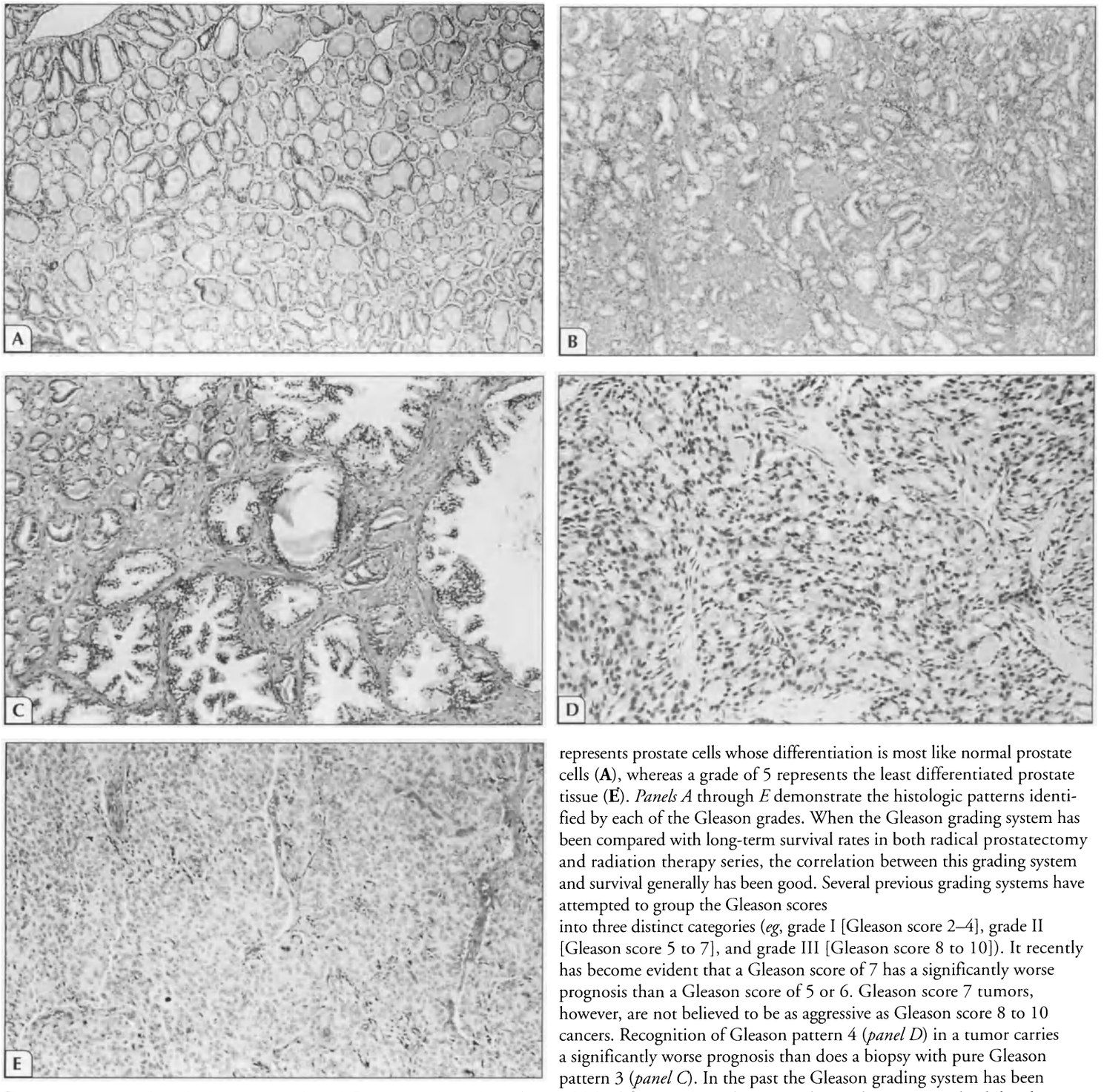


FIGURE 8-23. Histologic representation of Gleason grades 1 through 5. Various histologic grading systems for prostate cancer have been recommended over the years. One grading system, the Gleason grading system, has gained wide acceptance. This grading system is based primarily on the low-power glandular pattern of the tumor. Nuclear and cytologic features are not considered. The Gleason grading system assigns a grade from 1 to 5 for the primary (predominant) and the secondary (second most prevalent) architectural patterns identified within the tumor. A score of 1 represents prostate cells whose differentiation is most like normal prostate cells (**A**), whereas a grade of 5 represents the least differentiated prostate tissue (**E**). *Panels A* through *E* demonstrate the histologic patterns identified by each of the Gleason grades. When the Gleason grading system has been compared with long-term survival rates in both radical prostatectomy and radiation therapy series, the correlation between this grading system and survival generally has been good. Several previous grading systems have attempted to group the Gleason scores into three distinct categories (*eg*, grade I [Gleason score 2–4], grade II [Gleason score 5 to 7], and grade III [Gleason score 8 to 10]). It recently has become evident that a Gleason score of 7 has a significantly worse prognosis than a Gleason score of 5 or 6. Gleason score 7 tumors, however, are not believed to be as aggressive as Gleason score 8 to 10 cancers. Recognition of Gleason pattern 4 (*panel D*) in a tumor carries a significantly worse prognosis than does a biopsy with pure Gleason pattern 3 (*panel C*). In the past the Gleason grading system has been criticized for poor interobserver and intraobserver reproducibility, but recent studies have documented improvements in interobserver and intraobserver reproducibility (agreement within 1 Gleason sum). At this time, the Gleason scoring system represents the best prognostic marker available for clinically localized adenocarcinoma of the prostate. Careful understanding and recognition of the histologic patterns of this grading system are critical for urologists studying the clinical aspects of prostate cancer.

New Prognostic Markers Under Consideration

Cancer cell markers
- HER-2/neu
- Vascular endothelial growth factor
- FGF-8
- Basic FGF
- TGF-β_1
- Nm-23 H1
- IL-8
- Matrix metalloproteinases
- E-cadherin
- WAF1/CIP1 (p21)
- Stromal-epithelial hyaluronic acid
- HYAL 1 hyaluronidase on stromal cells
- 67LR
- KAI 1
- Thymosin β15
- Caveolin-1
- Prostate stem cell antigen
- Prostate carcinoma tumor antigen-1
- Prostate tumor inducing gene-1
- Gravin/AKAP12
- CaT-like channel
- MAPKK4/SEK1

Circulating markers
- Serum chromogranin A
- Circulating PSA RNA detected by RT-PCR
- Plasma IL-6
- Plasma IL-6 receptor

Cancer cell characteristics
- DNA ploidy
- Percent S phase

FIGURE 8-24. New prognostic markers in prostate cancer. The ability to better predict which prostate cancer patients might benefit from primary curative therapy (prostatectomy or radiation therapy) with or without adjuvant hormone therapy, chemotherapy, or other modalities (*eg*, vaccines) would be of great value to physicians and patients. Although current prognostic parameters such as Gleason scores, prostate-specific antigen (PSA), and clinical stage are helpful, improvement in prognostication would be welcomed. As we better understand prostate cancer biology, a number of cancer and blood markers have emerged as potential candidates. Although many of these markers correlate with other prognostic markers, large multivariate analyses have not been completed, which is a barrier for implementation of these markers in the clinical setting. New molecular techniques promise the identification of markers that may help predict metastatic potential and biologic behavior. Further, these new markers may also prove to be targets for new therapeutic strategies. FGF—fibroblast growth factor; IL—interleukin; 67LR—67-kD laminin receptor; MAPKK4/SEK1—mitogen-activated protein kinase kinase 4/stress active protein/Erk kinase 1; RT-PCR—reverse transcriptase polymerase chain reaction; TGF-β_1—transforming growth factor-β_1; VEGF—vascular endothelial growth factor. (*Adapted from* Gpoalkrishnan *et al.* [27].)

CONCLUSIONS

Characteristics of Nonpalpable Prostate Cancer in the Prostate-specific Antigen Era

		*Patients, n (%)**	
Study	***Population***	***Potentially Unimportant†***	***Potentially Significant‡***
Humphrey *et al.* [28]	Screened (*n*=78)	18 (23)	60 (77)
Epstein *et al.* [29]	Referral (*n*=157)	41(26)	116 (74)

**Men with nonpalpable prostate cancer and PSA elevations.*
†Tumor < 0.5 cm^3 with no poorly differentiated components.
‡Tumor < 0.5 cm^3, or tumor with poorly differentiated components.

FIGURE 8-25. Characteristics of nonpalpable prostate cancer in the prostate-specific antigen (PSA) era. Most prostate cancers detected (> 70%) are nonpalpable and are detected by prostate needle biopsy of the peripheral zone in men suspected of prostate cancer based on PSA elevations. The widespread use of PSA testing has led to earlier detection of prostate cancers before they can be felt on digital rectal examination, and this has resulted in virtual elimination of metastatic disease in serially screened populations. However, about 25% of nonpalpable cancers detected with PSA testing are potentially unimportant (< 0.5 cm^3 with no poorly differentiated elements), and it may not be necessary to treat them aggressively, especially in older men. Identification of those men with significant tumors (> 0.5 cm^3 or with poorly differentiated elements) that need aggressive treatment is an important challenge in the PSA era [28].

Criteria for Prediction of a Significant Tumor

Criteria	*Observations Predictive of a Significant Tumor*
PSA density	≥ 0.1
Pathology of needle biopsy	
Grade	Gleason score ≥ 7
Cores with cancer, *n*	≥ 2 involved
Percentage of core with cancer	≥ 50% involved

FIGURE 8-26. Prostate cancer detectable by prostate-specific antigen (PSA). The pretreatment criteria based on PSA density and needle biopsy findings are predictive of a significant cancer in men who have a PSA-detected nonpalpable prostate cancer. If the PSA density (PSA divided by ultrasound-determined prostate size) is 0.1 or greater, or if there is unfavorable pathology on needle biopsy (Gleason score 7 or higher, or more than two cores involved, or involvement of 50% or more), then 86% of the men will have a tumor larger than 0.5 cm^3 (significant cancer). If none of the above observations predictive of a significant cancer are present, 79% of men will have a tumor smaller than 0.5 cm^3 with no poorly differentiated elements (potentially insignificant cancer). For those men thought to have potentially insignificant cancers, expectant management or watchful waiting may be a reasonable option. (*Adapted from* Epstein *et al.* [29].)

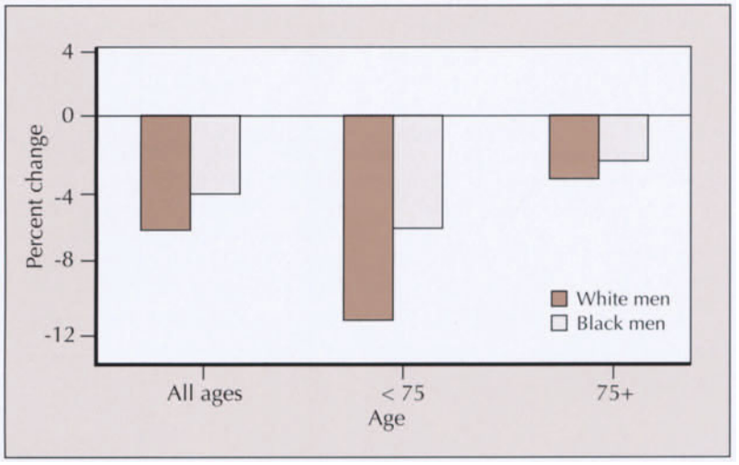


FIGURE 8-27. Prostate cancer mortality after a decade of prostate-specific antigen (PSA) testing and American Cancer Society Prostate Cancer Screening Guidelines. The American Cancer Society recently convened a multidisciplinary conference to evaluate the guidelines for screening for prostate cancer. The following statement summarizes the American Cancer Society's position in 1997 [30] regarding screening for prostate cancer:

"Both prostate-specific antigen (PSA) and digital rectal examination (DRE) should be offered annually, beginning at age 50 years, to men who have at least a 10-year life expectancy, and to younger men who are at risk. Information should be provided to patients regarding potential risks and benefits of intervention."

These recommendations highlight the interaction between physicians and patients regarding the need for prostate cancer screening. A full understanding of the potential risks, benefits, and further laboratory and diagnostic testing that will follow should these screening tests be abnormal must be discussed. It is also important to note that the American Cancer Society now recommends screening only for men who have a life expectancy of at least 10 years. High-risk groups also are now identified (*eg*, familial history, African-American descent), and earlier screening is recommended for these high-risk groups. The American Cancer Society also has pointed out that screening for prostate cancer in asymptomatic men has led to a decrease in the detection rate of advanced stage cancers. There has also been a reduction in mortality from prostate cancer in the United States; this, however, cannot be directly related to prostate cancer screening. The American Cancer Society currently recognizes an abnormal PSA value (> 4.0 ng/mL) and an abnormal DRE as abnormal results requiring further diagnostic evaluation.

Prostate cancer mortality has decreased for the first time 10 years after the introduction of a test (PSA) that has greatly decreased the presence of metastatic disease in a serially tested population. In the next decade, population data may reveal more substantial decreases in mortality among those more intensively screened (*eg*, white vs African-American men), similar to the data that now support routine cervical cancer screening. (*Adapted from* National Center for Health Statistics [31].)

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9

Decision Making for Clinically Localized Prostate Cancer

Michael W. Kattan & Brian J. Miles

Treatment decision making for patients with clinically localized prostate cancer can be difficult. Because of the age of men at diagnosis, survival benefits associated with aggressive therapies such as surgery typically are estimated to be small, and patient preferences are very influential in determining the preferred treatment. This chapter reviews two different methods for assisting patients in choosing the treatment that is best for them. First, we consider the decision analytic approach, which directly incorporates patient preferences and survival estimates in suggesting the appropriate treatment. Because this approach is difficult to perform at the bedside, we also discuss a second method, nomograms, which are mathematical models that predict outcomes for the individual patient.

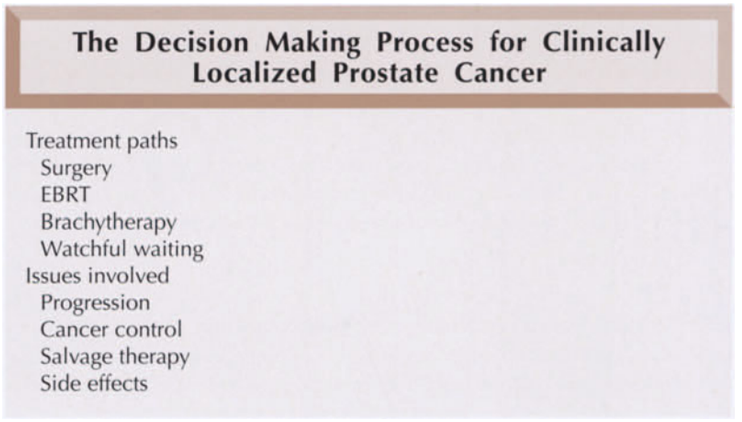


FIGURE 9-1. The decision-making process for clinically localized prostate cancer. The patient with clinically localized prostate cancer faces a daunting decision. He has one of three mainstream paths from which to choose: surgery, external beam radiation therapy (EBRT), and brachytherapy. Alternatively, he may decide to "stay put" for a while (watchful waiting). For the most part, he is basing his decision on four issues: 1) whether his cancer will progress if left untreated, 2) how well an aggressive therapy would control his cancer, 3) the ability of a salvage therapy in the event that primary therapy fails, and 4) the side effects of each therapy. For the individual patient, each of these criteria is fundamentally a prediction; no outcomes, good or bad, are known with certainty. Further, each man places different values on side effects (*eg*, impotence). Because of all these issues, treatment recommendations for the individual patient must be tailored to his disease and preferences.

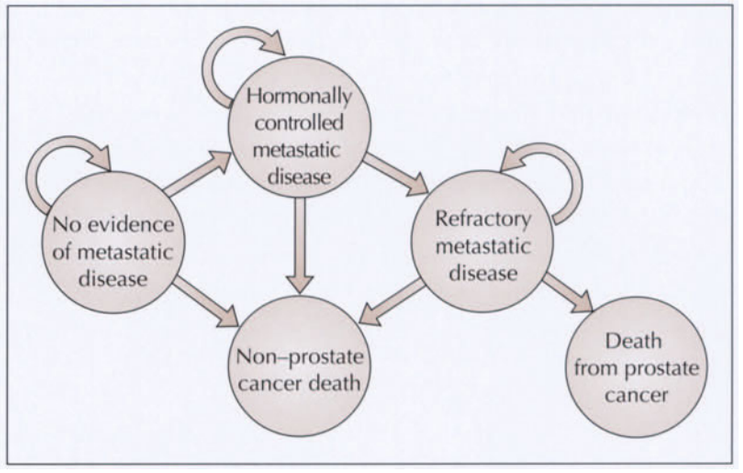


FIGURE 9-2. Most decision analyses use computerized Markov models to represent treatment decisions. These models move patients through various health states (*eg*, healthy, sick, and dead). This figure represents a Markov model for clinically localized prostate cancer [1]. In this example, a theoretical cohort of patients begins in the health state ("no evidence of metastatic disease") (*left*). Every 6 months, a fraction of the cohort is allowed to progress in the direction of the arrows. The probabilities of progression are taken from the literature. *Circular arrows* indicate that it is possible for the patient to remain in that health state at the end of a 6-month period. The two death states are absorbing; they cannot be exited. Computerized Markov models such as this one allow survival estimation for various treatment strategies. If we assume that the patient will not prefer all health states equally, we may then be able to estimate quality-adjusted life expectancy by assigning different weights to the different health states. The quality-of-life adjustments, called *utilities*, can be estimated using several established techniques. (*Adapted from* Kattan *et al.* [1].)

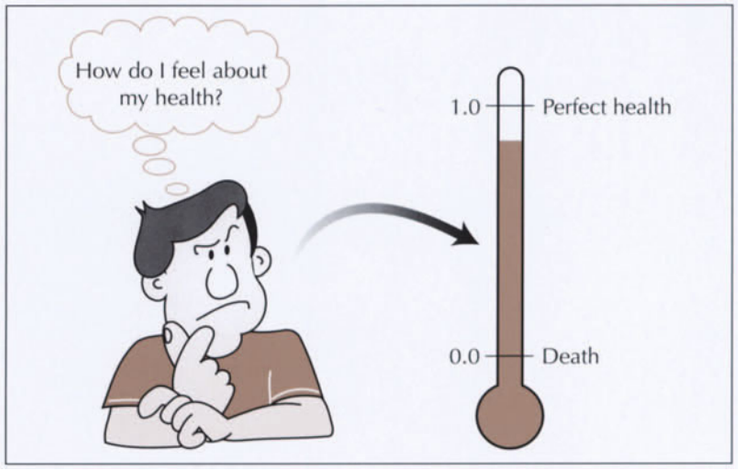


FIGURE 9-3. Quality of life (QOL). There are numerous definitions of QOL, from the psychologic to the social; in general, QOL can be understood as a patient's ability to function in a manner commensurate with his needs, desires, and abilities. Although all traditional definitions help us approach a "sense" of QOL, none can globally capture what it is for all people. QOL can be defined only by each individual. Therefore, measuring QOL has been viewed as an inexact science fraught with misinterpretation, overinterpretation, and biased or inadequate questioning. However, the science of QOL evaluation has progressed to such an extent that dependable and reproducible results that allow investigators to estimate a patient's QOL are achievable. For the purposes of decision algorithms and models, QOL measurement must be reported numerically, on a scale from 0 to 1, in which 0 represents "death" and 1 represents "perfect health." The value of a utility is that all health states can be placed in this common scale.

FIGURE 9-4. Utility assessment with the rating scale. We can measure quality of life in several ways, but we need a numeric scale for use in computing a decision analysis. A simple approach is to ask clinicians to rate various health states (*eg*, impotence) and use their collective estimate for quality of life. However, such a strategy will not likely be sensitive to the preference of the individual patient. Instead, it is better to ask the patient himself for how he would feel to have a particular complication. For example, we could ask the patient to place himself on a scale from 0 to 100. This is often called a "visual analog scale." It is easy to use, but it has an important limitation: the numeric score (*eg*, 90 of 100) does not have external meaning. What one patient considers a 90 may be very different from what another patient considers a 90.

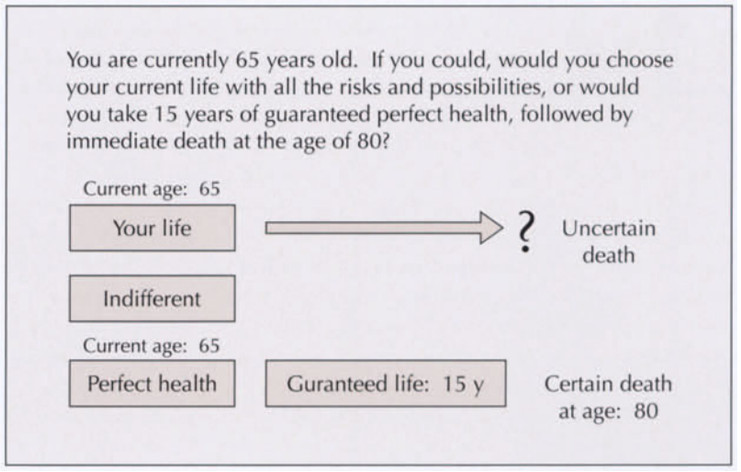


FIGURE 9-5. The time-tradeoff technique. One way of measuring utilities (*ie*, health state preferences) is to use the time-tradeoff technique. This is one of the most common utility assessment techniques. With this method, the patient chooses between his current health/life expectancy and a guaranteed period of perfect health followed by immediate death.

The duration of guaranteed perfect health is varied until indifference is reached, and utility is calculated as number of perfect health years divided by life expectancy. For example, patients might estimate the utility for impotence to be 0.8 and the utility for incontinence to be 0.7. This means that on average, patients would be willing to give up 10% of their life expectancy (0.8 − 0.7 = 0.1) to live with impotence rather than incontinence. Furthermore, a patient in this example would be willing to give up 20% of his life expectancy (1.0 − 0.8) to avoid impotence and remain in perfect health. As an example, the time-tradeoff technique works as follows for evaluating the utility for a person's current state of health. First, find the minimum amount of life in perfect health that the patient is willing to trade for his current life expectancy. Then divide the number of perfect health years by the life expectancy to obtain the utility for his current health state [2].

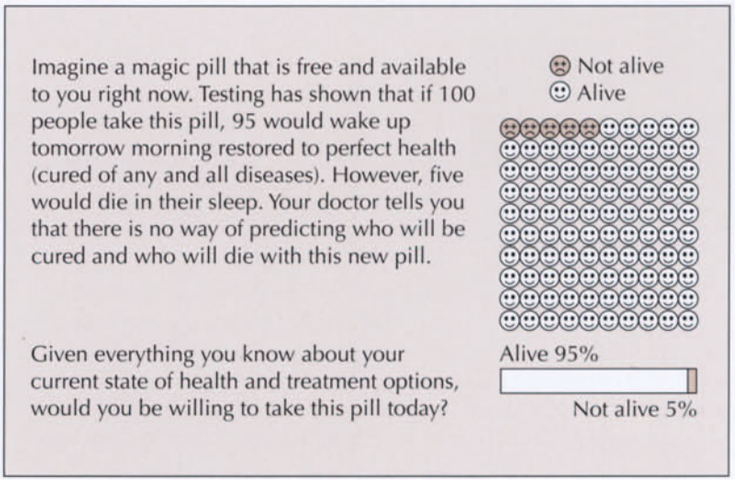


FIGURE 9-6. Another method of utility assessment: the standard gamble. The patient is asked to consider taking a make-believe pill that will either cure him of his health problems or kill him. Conceptually, this method is very attractive because the patient is providing a probability: the maximum probability of death that the patient is willing to risk in order to eliminate his current health problems. This method has surprisingly high patient comprehension and test-retest reliability.

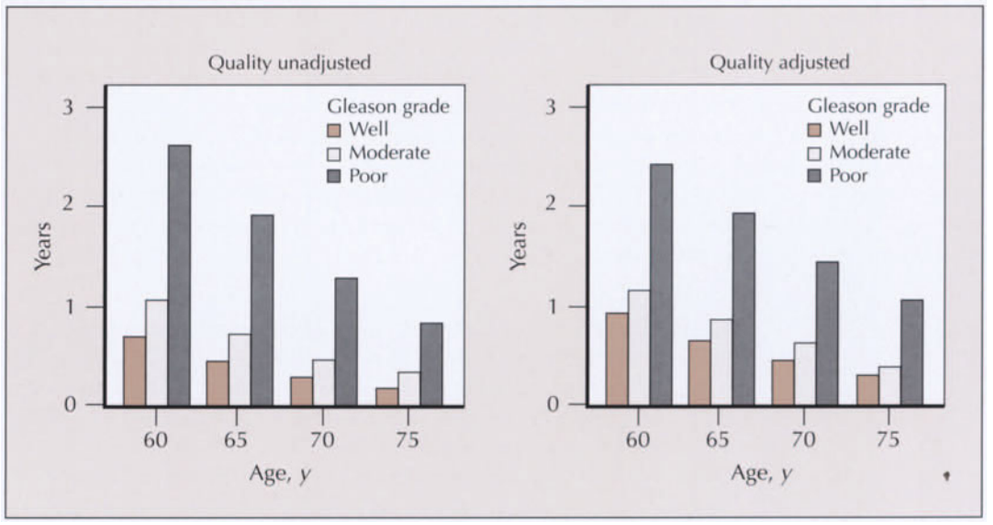


FIGURE 9-7. Quality-adjusted survival. Once we have developed the health states of interest in a Markov model and reviewed the literature to obtain the probabilities of moving from one health state to another, and the utilities of the health states, we can estimate survival and survival adjusted for quality of life under different treatment strategies. Quality-adjusted survival is survival probability multiplied by quality of life (utility). This figure compares quality-adjusted survival with unadjusted survival. The values on the bars indicate how many years longer a radical prostatectomy patient is expected to live than is a watchful-waiting patient. For example, a 60-year-old man with poorly differentiated disease who chooses radical prostatectomy is expected to live 2.58 years longer than had he chosen watchful waiting. After adjusting for quality of life impact, that same man is expected to live an excess of 2.43 quality-adjusted years. Note that these estimates assume the patient has no comorbidity, and they do not specifically consider a particular patient's utilities. Instead, these estimates use group mean utilities. This is an important limitation because individuals of a group do not necessarily share the same utilities. (*Adapted from* Kattan *et al.* [3].)

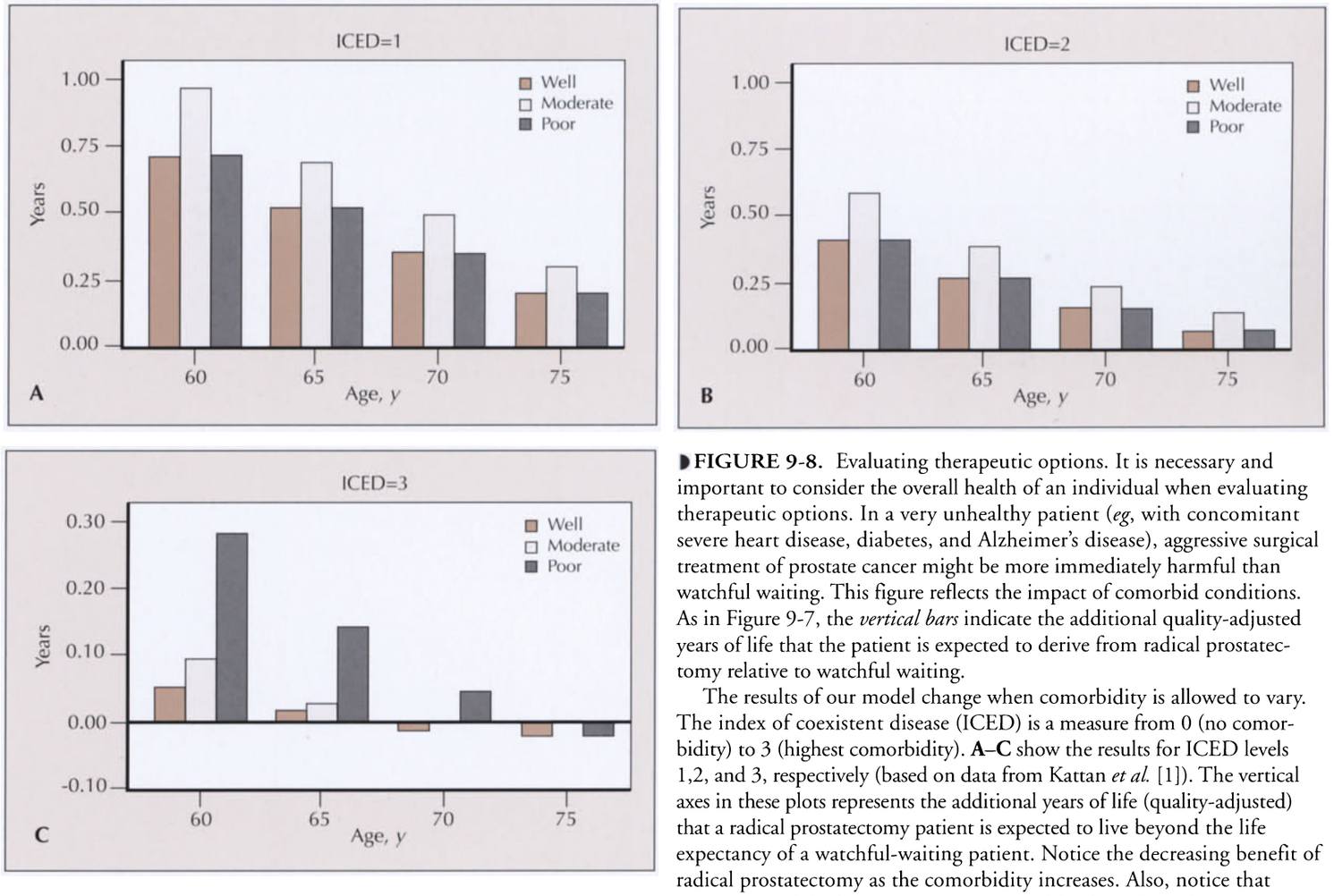


FIGURE 9-8. Evaluating therapeutic options. It is necessary and important to consider the overall health of an individual when evaluating therapeutic options. In a very unhealthy patient (*eg*, with concomitant severe heart disease, diabetes, and Alzheimer's disease), aggressive surgical treatment of prostate cancer might be more immediately harmful than watchful waiting. This figure reflects the impact of comorbid conditions. As in Figure 9-7, the *vertical bars* indicate the additional quality-adjusted years of life that the patient is expected to derive from radical prostatectomy relative to watchful waiting.

The results of our model change when comorbidity is allowed to vary. The index of coexistent disease (ICED) is a measure from 0 (no comorbidity) to 3 (highest comorbidity). **A–C** show the results for ICED levels 1,2, and 3, respectively (based on data from Kattan *et al.* [1]). The vertical axes in these plots represents the additional years of life (quality-adjusted) that a radical prostatectomy patient is expected to live beyond the life expectancy of a watchful-waiting patient. Notice the decreasing benefit of radical prostatectomy as the comorbidity increases. Also, notice that when comorbidity is very high, watchful waiting is preferred in older men with low-grade disease. Still, individual preferences need to be measured. Measuring individual utilities on each patient is time consuming and expensive, however. For this reason, we are developing software that assesses utilities, and allows the physician to enter clinical information and then compute the quality-adjusted survival estimates for that patient in a customized fashion (see our website: www.nomograms.org).

Partin Nomogram*

Gleason Score	PSA, 0.0–4.0 ng/mL — Clinical Stage							PSA, 4.1–10.0 ng/mL — Clinical Stage						
	T1a	T1b	T1c	T2a	T2b	T2c	T3a	T1a	T1b	T1c	T2a	T2b	T2c	T3a
Organ-confined Disease														
2–4	90 (84–95)	60 (72–86)	89 (88–92)	81 (75–86)	72 (65–79)	77 (69–83)	—	84 (75–92)	70 (60–79)	83 (78–88)	71 (64–78)	61 (52–69)	66 (57–74)	43 (27–58)
5	82 (73–90)	66 (57–73)	81 (76–84)	68 (63–72)	57 (50–62)	62 (55–69)	40 (26–53)	72 (60–85)	53 (44–63)	71 (67–75)	65 (51–60)	43 (36–49)	49 (42–55)	27 (17–39)
6	78 (68–88)	61 (52–68)	78 (74–81)	64 (59–68)	52 (46–57)	57 (51–64)	35 (22–48)	67 (55–82)	47 (38–57)	67 (64–70)	51 (47–54)	38 (34–43)	43 (38–49)	23 (14–34)
7	—	43 (34–53)	63 (58–68)	47 (41–52)	34 (29–39)	38 (42–45)	19 (11–29)	49 (34–88)	29 (21–36)	49 (45–54)	33 (29–38)	22 (18–26)	25 (20–30)	11 (6–17)
8–10	—	31 (20–43)	52 (41–82)	36 (27–45)	24 (17–32)	27 (18–36)	—	35 (18–62)	18 (11–28)	37 (28–46)	23 (16–31)	14 (9–19)	15 (10–22)	6 (3–10)
Established Capsular Penetration														
2–4	9 (4-15)	19 (13–20)	10 (7–14)	18 (13–23)	25 (19–32)	21 (14–28)	—	14 (7–23)	27 (18–37)	15 (11–20)	26 (19–33)	35 (25–43)	29 (21–37)	44 (30–59)
5	17 (9-26)	32 (24–40)	18 (15–22)	30 (26–35)	40 (34–46)	34 (27–40)	51 (38–65)	25 (14–36)	42 (32–51)	27 (23–30)	41 (36–46)	50 (45–55)	43 (37–50)	57 (45–68)
6	19 (11-29)	35 (27–43)	21 (18–25)	34 (30–36)	43 (38–48)	37 (31–43)	53 (41–85)	27 (15–39)	44 (35–53)	30 (27–33)	44 (41–48)	52 (48–56)	46 (40–51)	57 (47–67)
7	—	44 (35–54)	31 (26–36)	45 (40–50)	51 (46–57)	46 (38–52)	52 (40–63)	36 (20–51)	48 (38–60)	40 (35–44)	52 (48–57)	54 (49–59)	48 (42–54)	48 (37–58)
8–10	—	43 (32–56)	34 (27–44)	47 (38–56)	48 (40–57)	42 (33–52)	—	34 (17–58)	42 (28–57)	40 (33–49)	49 (42–57)	46 (39–53)	40 (31–48)	34 (24–46)
Seminal Vesicle Involvement														
2–4	0 (0-2)	1 (0–3)	1 (0–1)	1 (0–2)	2 (1–5)	2 (1–5)	—	1 (0–4)	2 (0–6)	1 (0–3)	2 (1–5)	4 (1–9)	5 (1–10)	10 (3–23)
5	1 (0-3)	2 (0–4)	1 (1–2)	2 (1–3)	3 (2–4)	3 (2–6)	7 (3–14)	2 (0–5)	3 (1–7)	2 (1–3)	3 (2–5)	5 (3–8)	8 (4–10)	12 (6–20)
6	1 (0-3)	2 (0–4)	1 (1–2)	2 (1–3)	3 (2–4)	4 (2–5)	7 (4–19)	2 (0–6)	3 (1–8)	2 (2–3)	3 (2–4)	5 (4–7)	6 (4–9)	11 (6–18)
7	—	8 (1–13)	4 (2–7)	6 (4–9)	10 (8–14)	12 (7–17)	19 (10–31)	6 (0–19)	9 (2–18)	8 (5–11)	10 (8–13)	15 (11–19)	18 (13–24)	26 (17–36)
8–10	—	11 (2–23)	9 (5–18)	12 (7–19)	17 (11–25)	21 (12–31)	—	19 (0–34)	15 (4–29)	15 (10–22)	19 (13–26)	24 (17–31)	28 (20–37)	35 (23–48)
Lymph Node Involvement														
2–4	0 (0-1)	0 (0–1)	0 (0-0)	0 (0–0)	0 (0–1)	0 (0–1)	—	0 (0–2)	1 (0–3)	0 (0–1)	0 (0–1)	1 (0–2)	1 (0–2)	1 (0–5)
5	0 (0-2)	1 (0–2)	0 (0-0)	0 (0–1)	1 (0–2)	1 (0–2)	2 (0–4)	1 (0–5)	2 (1–5)	0 (0–1)	1 (0–1)	2 (1–3)	2 (1–3)	3 (1–7)
6	1 (0-7)	2 (1–5)	0 (0-1)	1 (0–1)	2 (1–3)	2 (1–4)	5 (2–9)	3 (0–15)	5 (2–11)	1 (1–2)	2 (1–3)	4 (3–6)	4 (3–6)	9 (5–15)
7	—	6 (2–13)	1 (1-3)	2 (1–4)	5 (2–8)	5 (2–9)	9 (4–17)	8 (0–32)	12 (5–23)	3 (2–5)	4 (9–6)	9 (6–12)	9 (6–13)	15 (8–23)
8–10	—	14 (5–27)	4 (2-7)	5 (2–9)	10 (5–17)	10 (4–18)	—	18 (0–55)	23 (10–43)	8 (4–12)	9 (5–13)	16 (11–24)	17 (10–26)	24 (13–38)

*Numbers represent percent predictive probability (95% CI). Ellipses indicate lack of sufficient data to calculate probability.

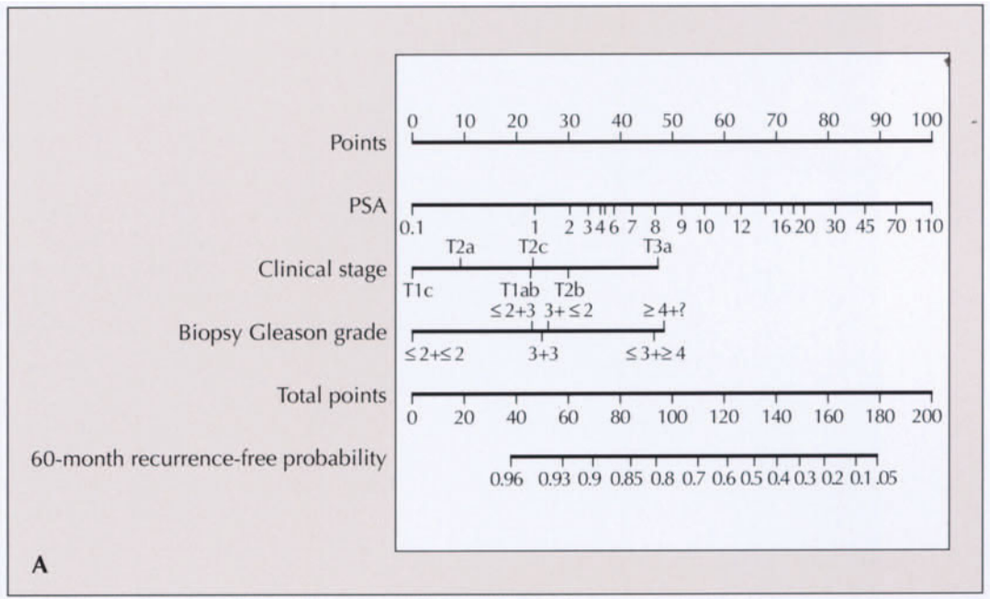
FIGURE 9-9. Nomograms. Markov's modeling is difficult to perform on individual patients [4]. Furthermore, Markov models are designed for use in population and cohort studies. Because of this difficulty of use, many physicians prefer to use nomograms. These are mathematical devices (usually tables or charts) that predict the probability of an outcome for an individual patient. The main attraction of a nomogram is that it precisely predicts probabilities, which is something that humans have difficulty doing. Numerous studies have shown that nomograms predict more accurately than do human experts under most conditions [3–6].

This figure shows the most popular nomogram for clinically localized prostate cancer: the original Partin nomogram. This table indicates the predicted probability that a man has either organ-confined, capsular penetration, seminal vesicle invasion, or lymph node–positive disease. To make this final pathologic prediction, the nomogram requires the measurement of a man's preoperative prostate-specific antigen level, clinical stage, and Gleason sum of the biopsy. The nomograms are based on logistic regression analyses of several thousand men treated at three different institutions. PSA—prostate-specific antigen. (*Adapted from* Partin *et al.* [7].)

Predictive Value of Pathologic Stage

Pathologic Stage Grouping	Probability of PSA Recurrence at 5 Years, %
Organ confined	10
Non–organ confined	50
Negative lymph nodes	20
Positive lymph nodes	88

FIGURE 9-10. Predictive value of pathologic stage. Although pathologic stage is an important endpoint to predict, it is difficult to interpret for prognostic purposes. Many patients and physicians believe that organ-confined concerns are always cured with surgery, and that non–organ-confined cancers (extracapsular extension or seminal vesicle invasion or positive lymph nodes) are never cured. Neither statement is true. Although organ-confined cancers have a high cure rate, as shown in this figure, approximately 10% will fail. More importantly, nearly half of all non–organ-confined prostate cancer fail to progress by 5 years. In other words, the probability of organ confinement cannot be considered the progression-free probability. Final pathologic stage fails to provide a crisp breakpoint above which cancers always recur. For this reason, it would be more valuable to predict prostate-specific antigen (PSA) recurrence as an endpoint. (*Adapted from* Kattan *et al.* [8].)



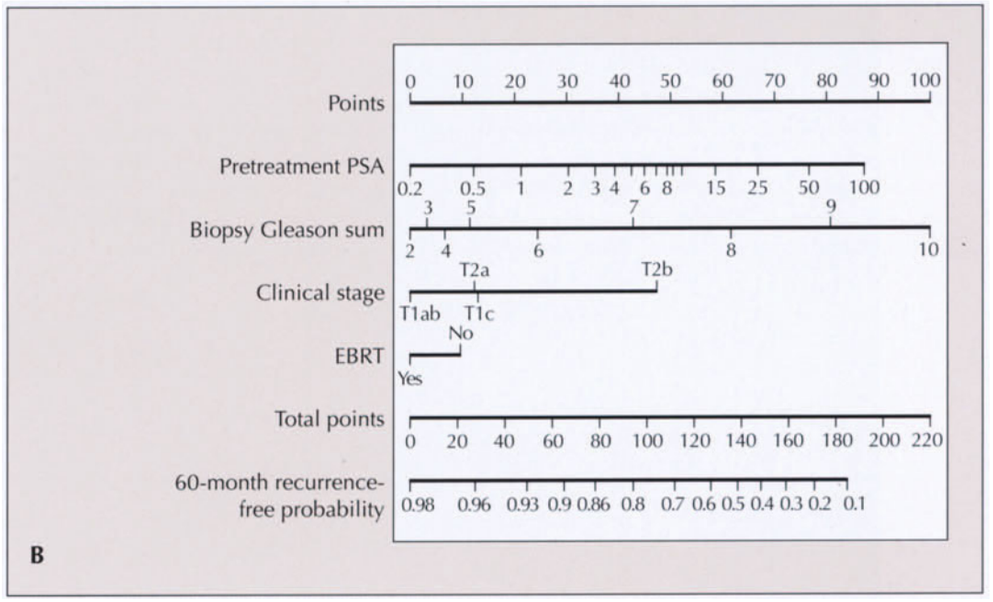


FIGURE 9-11. Nomograms for predicting prostate-specific antigen (PSA) recurrence within 5 years. Each of these tools predicts the probability that a man will experience PSA recurrence within 5 years of treatment, depending on whether or not he chooses surgery (**A**), brachytherapy (**B**), or external-beam radiation therapy (EBRT)

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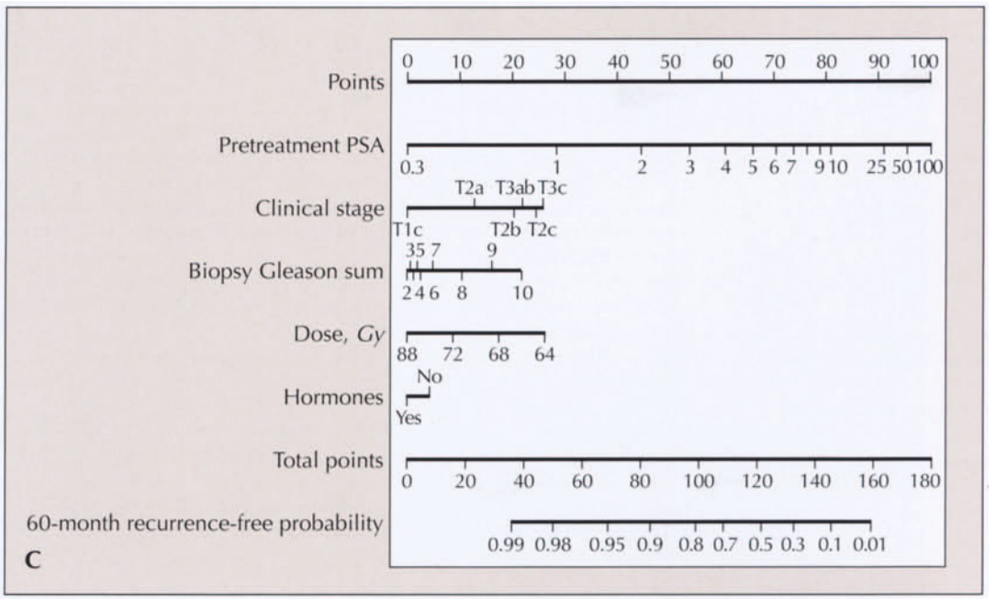

FIGURE 9-11. *(Continued)* (C). They are available on computer software available on-line at http://www.nomograms.org. (*Adapted from* Kattan *et al.* [9–11].)

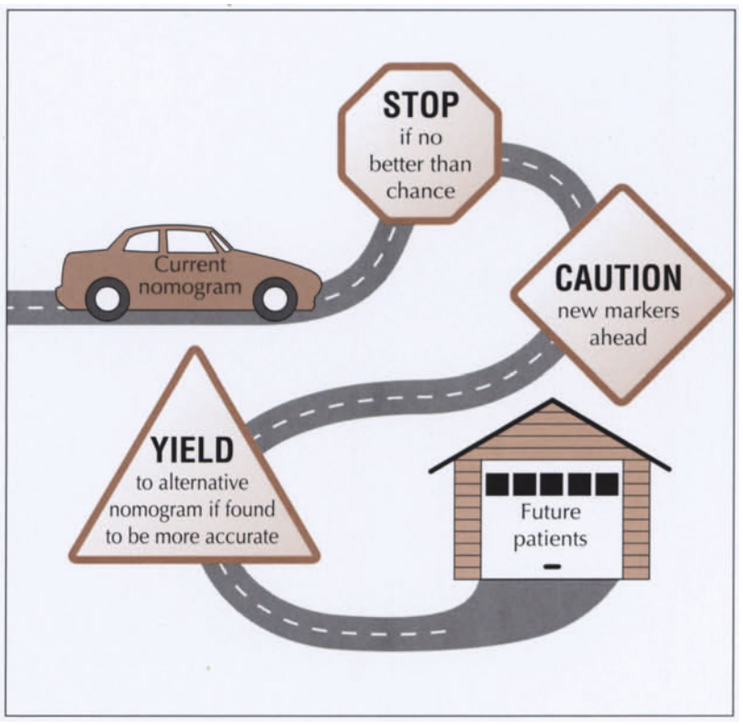

FIGURE 9-12. Nomograms are not without limitations. Because they always predict probabilities of an event that will either occur or not, nomograms are always wrong! New markers may come along in the future that will improve our ability to predict, rendering some nomograms obsolete. Certainly, if a nomogram does not predict better than chance, it will not be useful. However, an imperfect prediction from a nomogram is still of value to the decision maker if it is the most accurate prediction currently available [12].

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10

Radical Perineal Prostatectomy

Lorne D. Sullivan

Radical perineal prostatectomy has been widely practiced to cure selected cases of localized prostate cancer for many decades [1,2]. The long-term survival data and disease-free survival have been excellent [3–5]. The indications for radical perineal prostatectomy initially were confined to the lesion described as B1, less than 1 cm in size, and usually well differentiated.

In the 1970s it became apparent that staging pelvic lymph node dissection done before treatment of localized prostate cancer by brachytherapy was finding significant numbers of patients with positive lymph nodes [6]. Similar results were found with pelvic lymph node dissection before radical prostatectomy in patients whose localized prostate cancer did not conform to the classic B1 lesion, leading to the inclusion of pelvic lymph node dissection before radical prostatectomy as a staging criterion at many centers. Because the lower abdomen was opened for the pelvic node dissection, it was logical to proceed directly to retropubic prostatectomy; many centers moved away from the perineal approach.

With the introduction of the prostate-specific antigen (PSA) test and an increased public awareness of treatment options for localized prostate cancer during the past decade, we have seen a major change in the staging of patients presenting as possible candidates for radical prostatectomy [7].

Several authors recently identified groups of patients presenting with localized prostate cancer who are at extremely low risk for positive lymph nodes [8–10]. Laparoscopic ileo-obturator node dissection may be performed as a separate procedure in doubtful cases [11] Nerve-sparing techniques by the perineal route with reasonable preservation of potency have been described by several authors [12].

These developments and the perceived advantages of radical perineal prostatectomy (*ie*, less invasive exposure, short operating time, minimal use of analgesics, early return to ambulation and oral intake, excellent hemostasis and minimal requirement for blood transfusions, early discharge from hospital) have prompted continued interest in the radical perineal prostatectomy. This chapter presents the surgical procedure and results [13,14].

Indications for Radical Perineal Prostatectomy

Usual indications
- Clinically localized prostate carcinoma on
  - Digital examination
  - Sextant rectal ultrasound (TRUS)–guided biopsies
- Ten-year life expectancy (< 70 years of age)
- Minimal comorbidity
- Gleason scores < 8 (4+4)
- PSA level < 10 ng/mL

Unusual indications
- Gross obesity
- Previous multiple abdominal procedures
- Previous abdominal perineal surgery
- Previous arterial bypass grafts in the pelvis
- Previous extensive transurethral prostatic resection
- Salvage prostatectomy with delayed recurrence after radiotherapy

FIGURE 10-1. Indications for radical perineal prostatectomy. All of the usual indications must be present before radical perineal prostatectomy is considered. In cases in which the prostate-specific antigen (PSA) level is greater than 10 and the Gleason score is 5 or above on any single biopsy specimen, a radical perineal prostatectomy may be offered only after negative results have been obtained on an ileo-obturator node dissection and on a bone scan (patients undergoing a node dissection often opt for concurrent radical retropubic node dissection under the same anesthetic).

Nerve sparing is offered to carefully selected patients who have normal preoperative sexual function and do not have a positive apical biopsy on the same side as the nerve to be spared, who have fewer than two positive biopsy results on the same side without evidence of capsular extension, and who have no Gleason 5 involvement on the ipsilateral side on biopsy analysis. Patients who normally would be considered candidates for retropubic prostatectomy sometimes are referred for the perineal approach because of unusual circumstances that make it more appropriate than the retropubic approach.

Preoperative Considerations

Preoperative work-up
- Medical evaluation: history, physical examination, and assessment of life expectancy
- Standard blood work
- Electrocardiogram
- PSA
- DRE
- Six zonal transrectal ultrasound–guided biopsies
- Ileo-obturator node dissection (recommended for selected cases; see Fig. 10-1)
- Blood type and screen (no cross-match)

Preoperative preparation of patient
- Bowel preparation (usually PEG) given at home the day before surgery
- Preoperative intravenous antibiotics, including cefazolin sodium; gentamicin, 1 mg/kg; and metronidazole, 500 mg. These are given on arrival in the preanesthetic area.

FIGURE 10-2. Preoperative considerations. The preoperative work-up involves blood work, biopsies, and a node dissection, if necessary. Because blood transfusions rarely are needed, only a type screen is done so that matched blood can be available within 20 minutes, if needed. If patients prefer autologous blood collection, two units can be stored. In a study comparing radical perineal prostatectomy with retropubic prostatectomy at our center, only one of 79 perineal patients required blood transfusion, and that patient was found to have von Willebrand's disease [14].

Preoperative preparation is done at home the night before the surgery, because the patient can be admitted on the day of surgery and already will have been seen at a preoperative assessment clinic. Minimal preanesthetic preparation is required. Blood loss usually averages 400 mL or less [14], and extensive monitoring lines are not necessary, obviating the need for invasive anesthesia. DRE—digital rectal examination; PSA—prostate-specific antigen; PEG—polyethylene glycol.

Postoperative Care

Ambulation on arrival to the ward
Analgesia as required (usually minimal, oral)
Oral fluids on first postoperative day; full fluids to soft diet on second postoperative day
Removal of Penrose drain on first or second postoperative day
Discharge on first postoperative day
Removal of Foley catheter 3 weeks postoperative
Follow-up assessment, including PSA levels, at 1, 3, 6, and 12 mo postoperation and once a year thereafter

FIGURE 10-3. Postoperative considerations. The postoperative care of the radical perineal prostatectomy patient is very straightforward. Patients should be encouraged to ambulate and start oral fluids the same day as the operation. Intravenous fluids are given until the patient is drinking adequate amounts. Minimal analgesia usually is required, although many patients may need one intramuscular injection of narcotic analgesia in the recovery room. Early discharge is possible as soon as the patient is stable, usually on the morning of the first postoperative day after review by the surgeon. PSA—prostate-specific antigen.

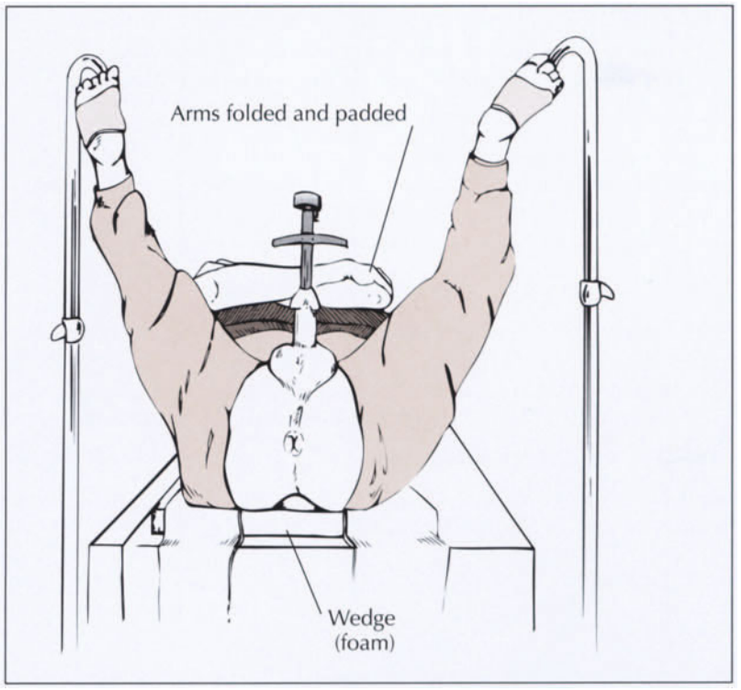
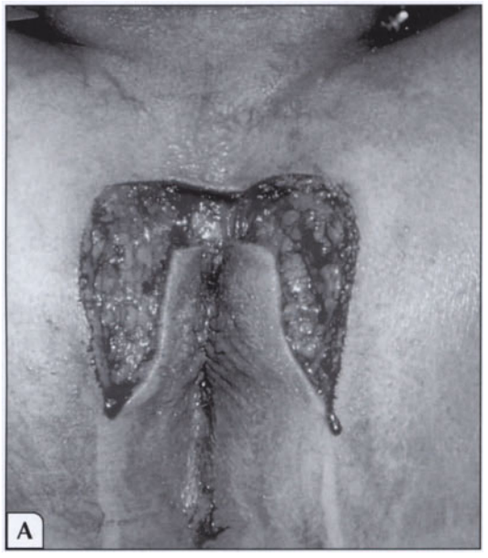


FIGURE 10-4. Patient positioning. The patient is positioned in an exaggerated lithotomy position, using a standard operating table, shoulder support, and leg stirrups. The arms are folded over the chest and padded to avoid brachial plexus traction. A curved Lowsley retractor is inserted transurethrally, prior to incision of the skin. The "blades" are opened. (*Adapted from* Sullivan *et al.* [13].)



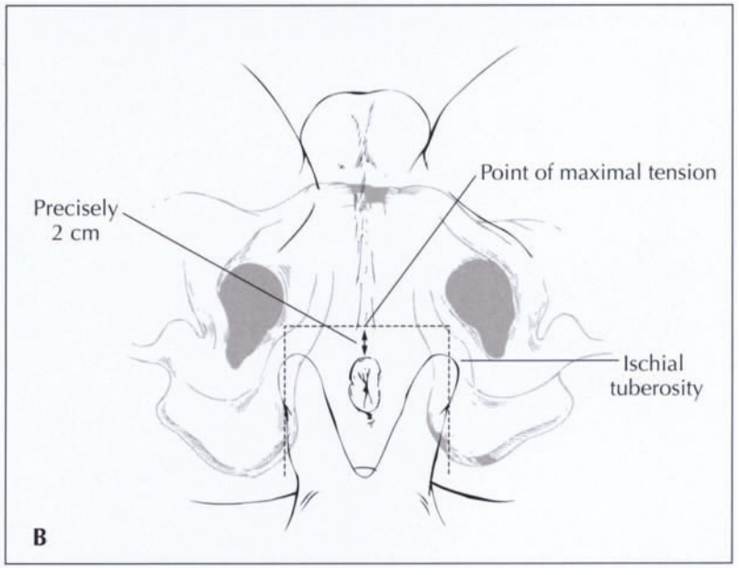


FIGURE 10-5. Incision. **A** and **B,** An inverted "U" incision should be made between the ischial spines exactly 2 cm anterior to the anal verge. The incision site can be confirmed by retraction of the skin bilaterally over the ischial spines. This method tents the skin over the subcutaneous anal sphincter, forming a defined line for the incision. The incision is carried posteriorly on either side. (**B** *adapted from* Paulson and Thrasher [15].)

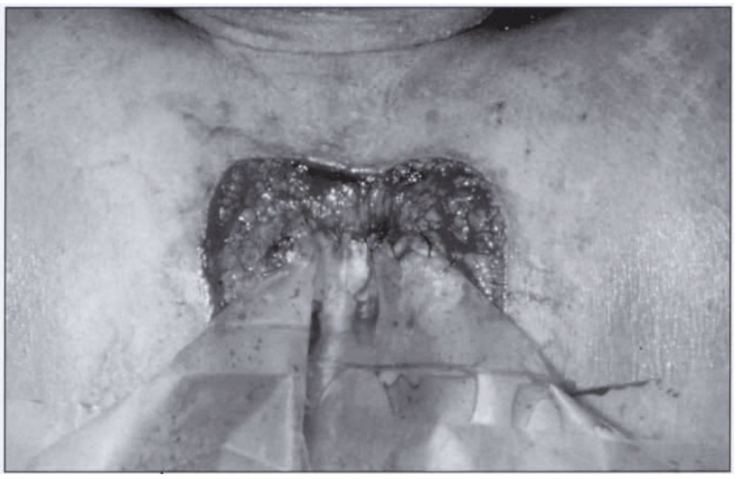
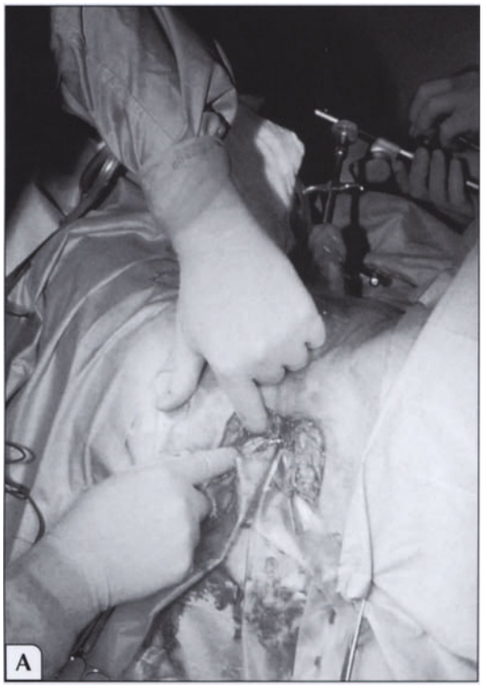


FIGURE 10-6. Placement of sterile O'Connor drape. A lubricated O'Connor shield is sutured to the lower wound edge, providing sterile rectal access and allowing intraoperative assessment of the dissection.



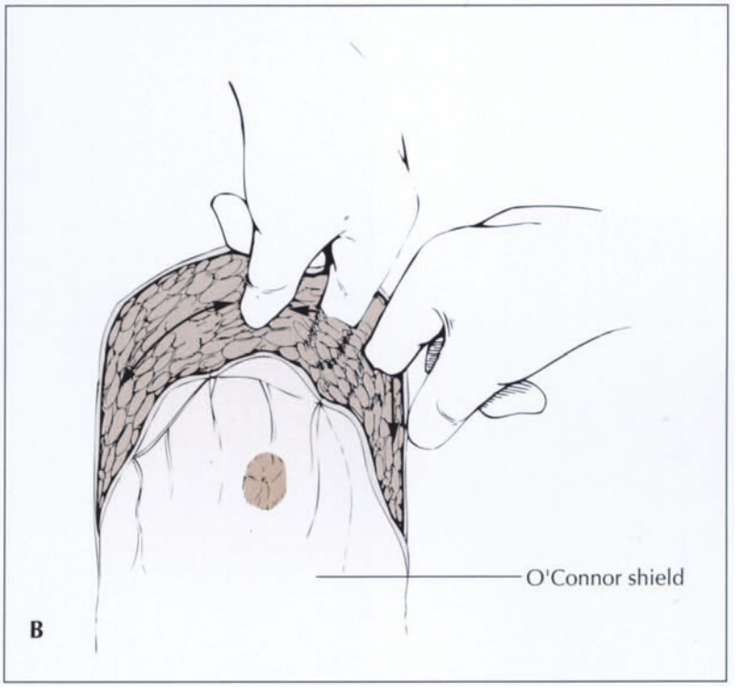
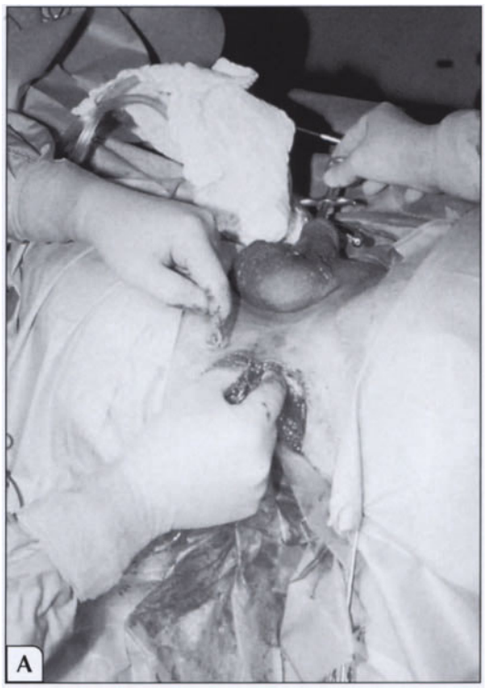


FIGURE 10-7. Dissection. **A** and **B,** Incision and blunt dissection of ischiorectal fat. Sharp dissection is used to develop the ischiorectal fossae on either side of the anus. The superficial fasciae is then incised at a 35° angle from the midline, causing the fat of the ischiorectal fossae to "bulge out." Blunt dissection of the remainder of the fossa can be performed by placing both index fingers into the fossa and dissecting superiorly and inferiorly until enough space is provided. Traction on the pudendal nerves and vessels in the apex of the fossa should be avoided. (**B** *adapted from* Sullivan *et al.* [13].)



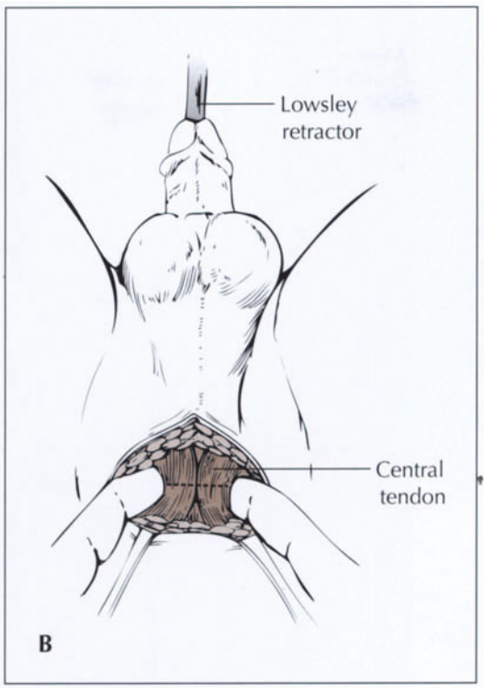
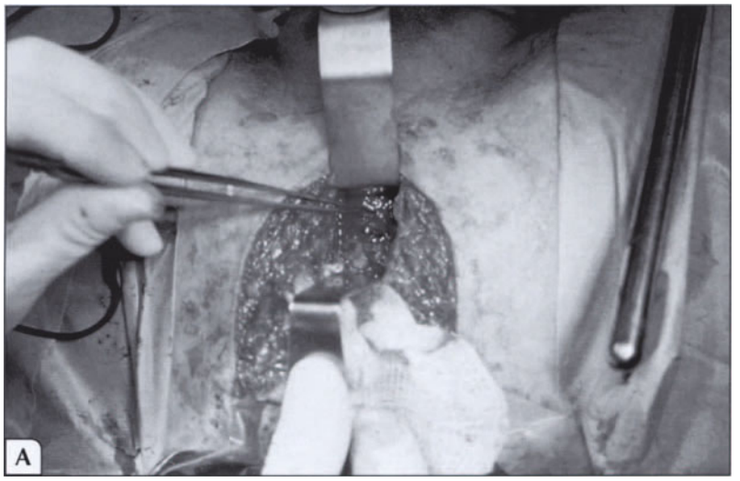


FIGURE 10-8. Incision of the central tendon. **A**, The index finger and thumb are used to pinch the tissue in front of the anus and behind the central tendon of the perineum. This creates a safe space behind the tendon. **B**, The tendon can then be incised using cautery (*dotted line*). (**B** *adapted from* Paulson and Thrasher [15].)



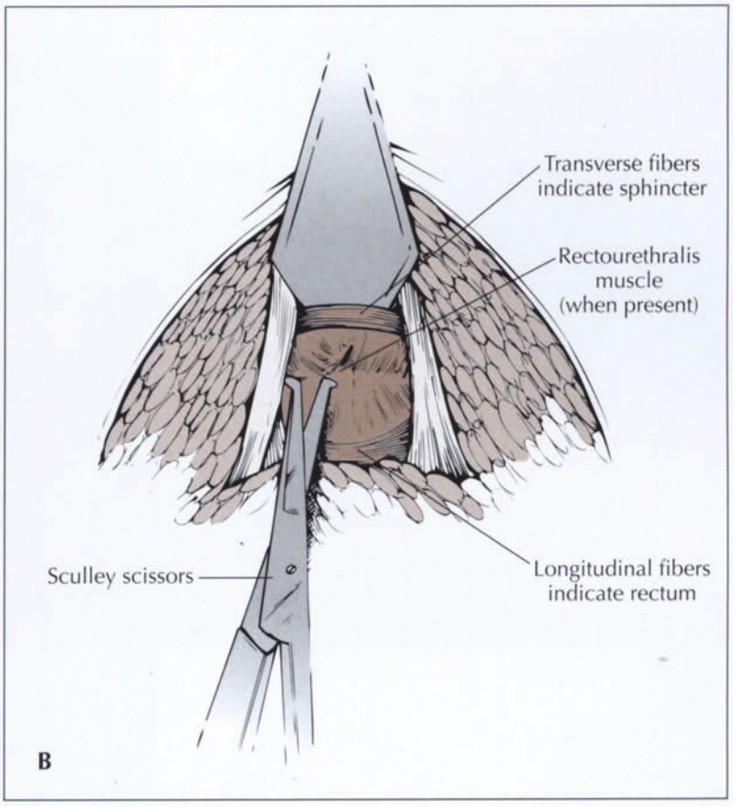
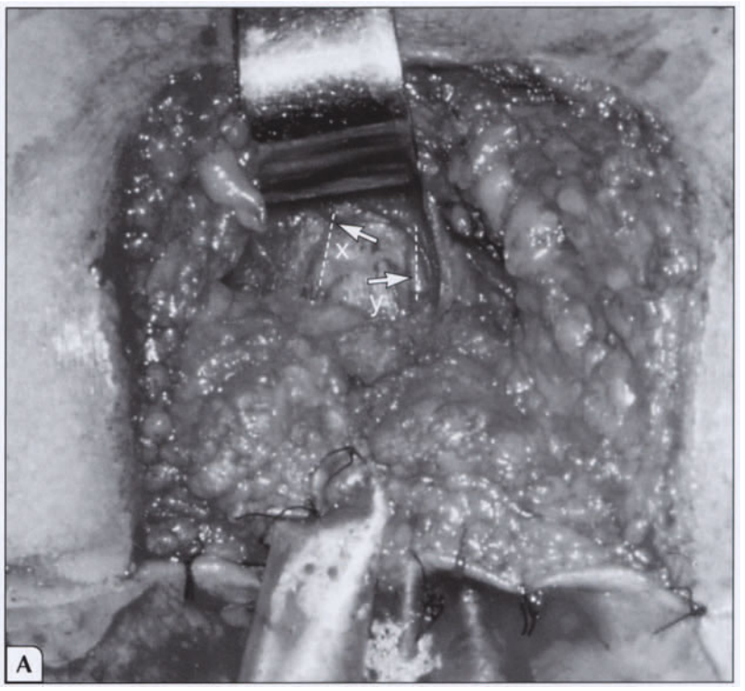


FIGURE 10-9. Dissection continued. **A** and **B**, Sharp dissection along *longitudinal* rectal fibers to *horizontal* fibers of striated sphincter. Horizontal fibers of the external anal sphincter run above the longitudinal rectal fibers and can be readily identified. This junction identifies the transsphincteric approach. Sculley scissors are used to perform a precise dissection along the rectal plane (longitudinal fibers). A retractor is used anteriorly to expose the striated urinary sphincter. The horizontal striated muscle fibers of the urethral sphincter complex are *precisely* elevated from the longitudinal rectal fibers to expose the apex of the prostate. The prostate can be rotated side to side with the curved Lowsley retractor to bring the prostate closer to the perineum, thus aiding visualization. Sharp and blunt dissection are used to dissect the posterior prostate from the rectum. If the perineal exposure allows, the surgeon has the advantage of taking a wide margin in selected cases, including, if necessary, the anterior rectal fascia, the neurovascular bundles, and even some levator fibers can be left covering the prostate. (**B** *adapted from* Sullivan *et al.* [13].)



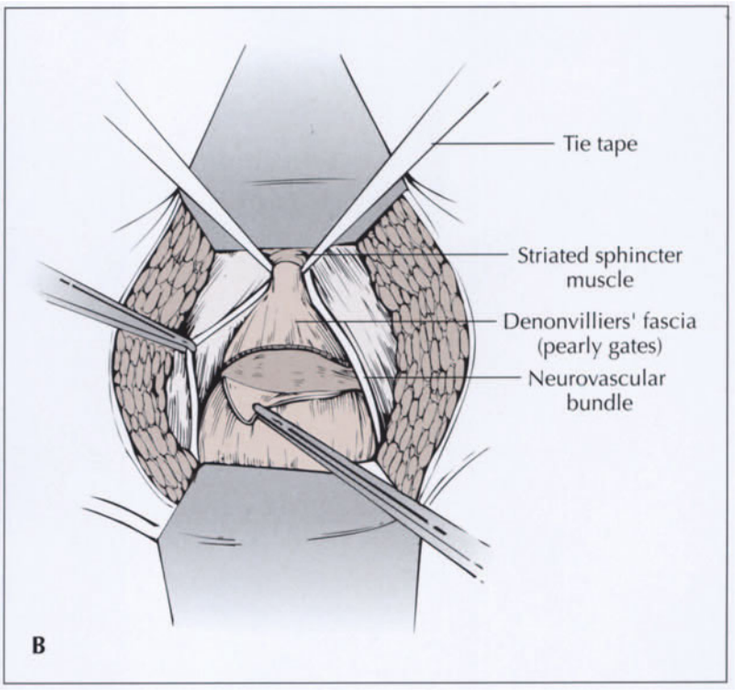


FIGURE 10-10. Excision or preservation of neurovascular bundles and incision of posterior urethra. **A**, A Penfield dissector is used to dissect the neurovascular bundles from the posterior prostate (*x* and *y*). These can be resected widely with the prostate or conserved (see Figs 10-24*B* and 10-24*C*). Isolation of the neurovascular bundles may be performed in most cases. **B**, During the perineal approach to radical prostatectomy, care should be taken to prevent neuropraxia related to retraction. Neurovascular bundles may be difficult to isolate or identify in some cases, particularly after transurethral resection of the prostate or irradiation. (**B** *adapted from* Weldon and Tavel [12].)

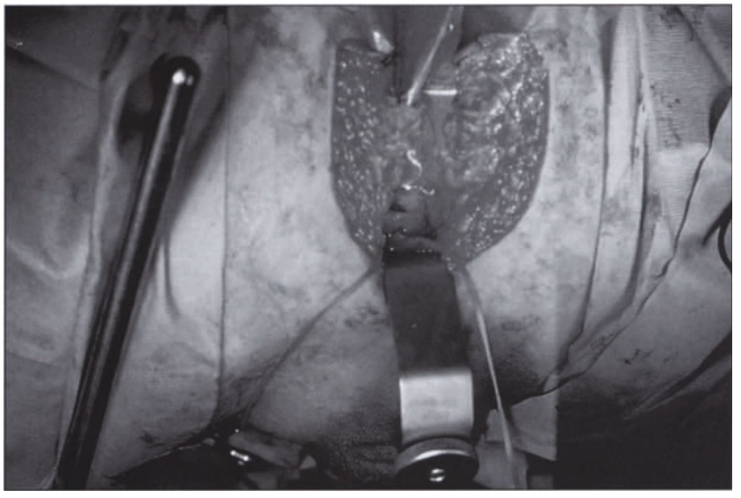


FIGURE 10-11. Continuation of procedure. A Lauer forceps is passed around the urethra, and an umbilical tape is placed.

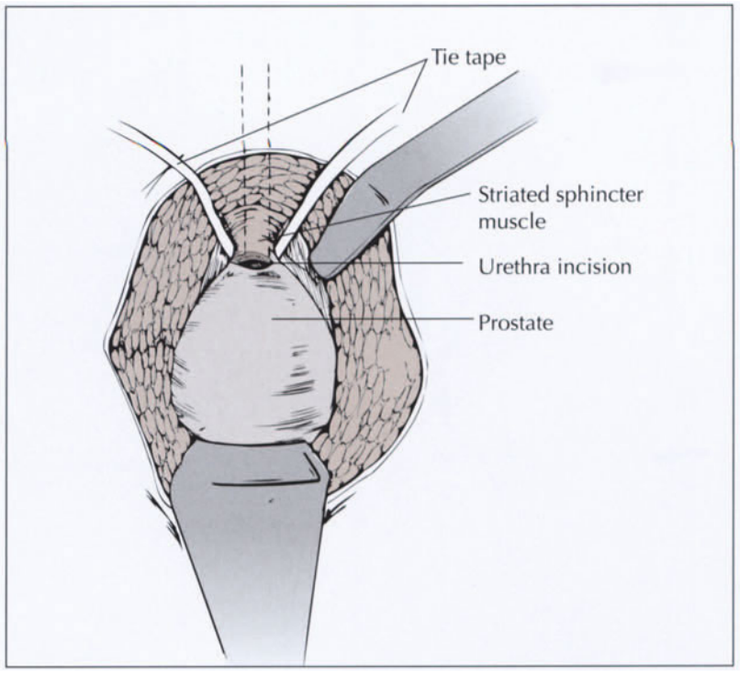


FIGURE 10-12. Division of urethra. The anterior (ventral) urethra is divided precisely at the junction with the prostate. Rush sections of the prostate apex are taken to confirm negative margins. The straight Lowsley retractor is placed into the urethra and the blades opened inside the bladder. The posterior (dorsal) urethra is precisely divided, preserving urethral length and the entire urethral sphincter mechanism. Gentle traction is applied to depress the prostate into the incision. (*Adapted from* Hudson [16].)

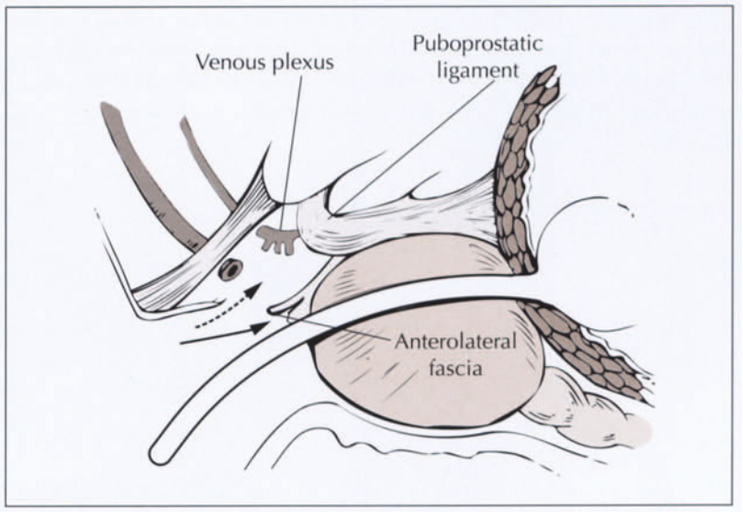


FIGURE 10-13. Retropubic dissection. Shown is the proper plane of dissection (*solid arrow*) beneath the anterolateral fascia and beneath the venous plexus. Dissection above this fascia (*dotted arrow*) may disrupt the venous sinus and cause significant bleeding [13]. Blunt dissection of the anterior prostate away from the puboprostatic ligaments is performed. In patients with transitional zone carcinoma, where wide margins are required, sharp dissection is used. (*Adapted from* Paulson and Thrasher [15].)

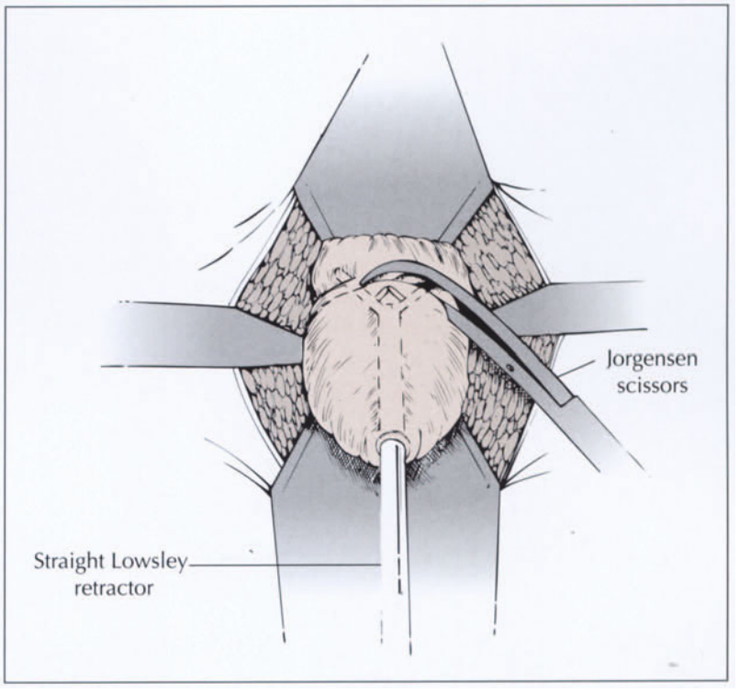


FIGURE 10-14. Lauer forceps are used to take the lateral pedicle of the prostate, including the prostatic arterial supply. These maneuvers facilitate homeostasis and retraction of the prostate into the incision. The blades of the Lowsley retractor become palpable at the bladder neck, and Jorgensen scissors are used to precisely incise the bladder neck. In patients with transition zone cancer, a cuff of anterior bladder neck may be taken with frozen sections to ensure a negative margin. (*Adapted from* Sullivan *et al.* [13].)

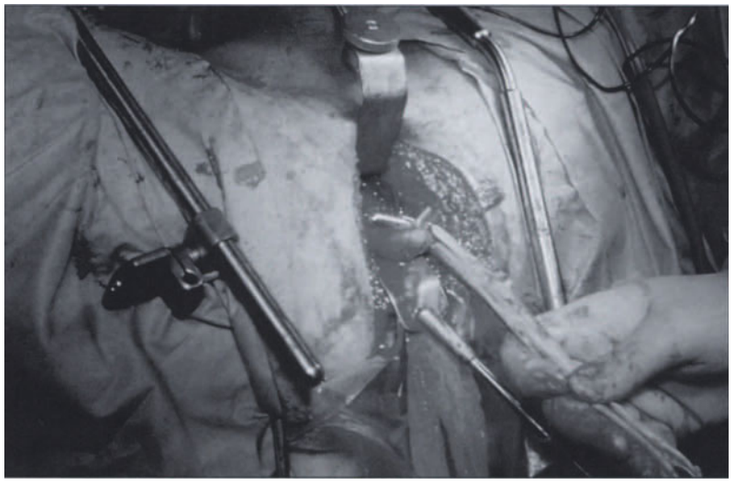


FIGURE 10-15. Continuation of procedure. The Lowsley blades are then repositioned anterior to the bladder neck, exposing the trigone.

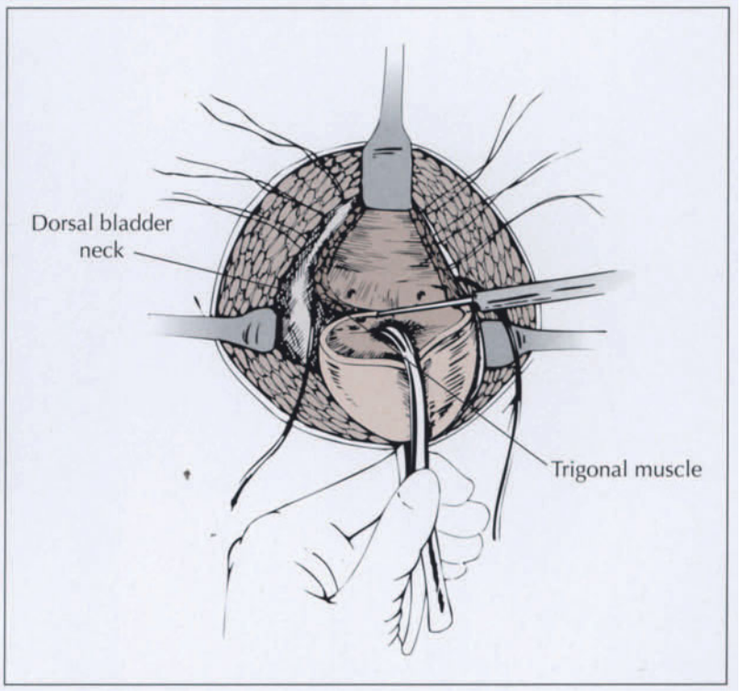


FIGURE 10-16. Incision of the trigone. The trigone and the posterior bladder neck are incised under direct vision. Care must be taken to avoid the ureteric orifices. One ampule of indigo carmine is given intravenously before incision of the trigone. If indigo carmine is unavailable or the ureteric orifices are difficult to see, 4- or 5-F urethral catheters can be inserted. (*Adapted from* Hudson [16].)

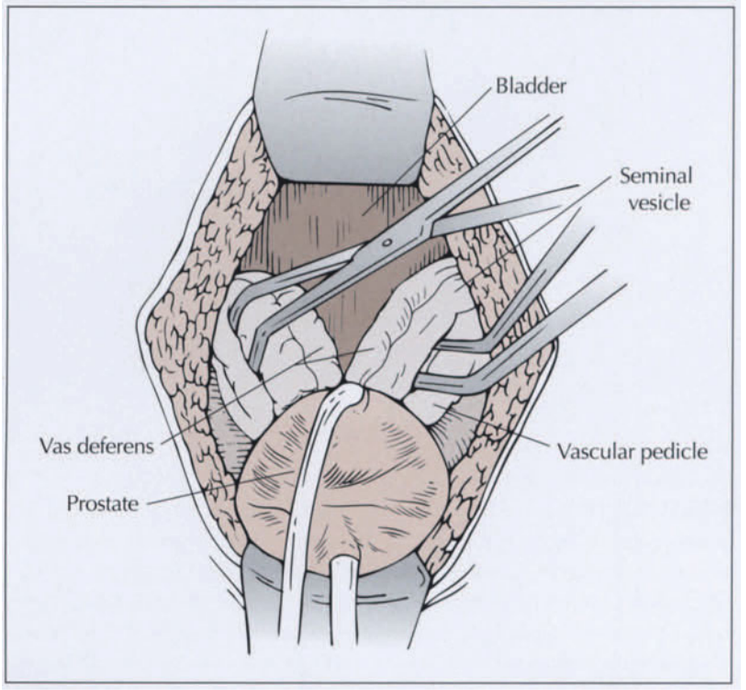


FIGURE 10-17. Completion of dissection of pedicles, ejaculatory ducts, and seminal vesicles. Dissection is carried posteriorly, and seminal vesicles and ampullae of the vas deferens are dissected, clipped, and excised. Adequate retraction is essential. Parker or Deaver retractors may be needed to facilitate exposure and complete removal of the vesicles. Care is taken to avoid rectal or trigonal injury or traction on the neurovascular bundles if nerve sparing is a priority. (*Adapted from* Paulson and Thrasher [15].)

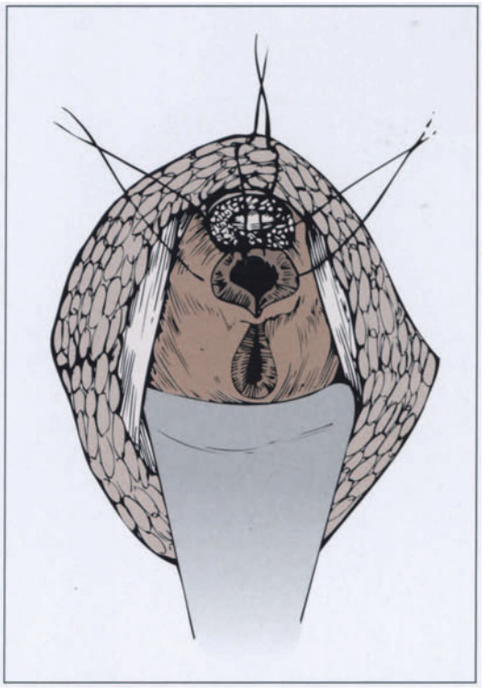


FIGURE 10-18. Bladder neck reconstruction. The posterior bladder neck is closed with interrupted 2-0 chromic sutures, and the mucosa is everted over the bladder neck muscle and then closed with 4-0 chromic sutures to cover the bladder neck. (*Adapted from* Hinman [17].)

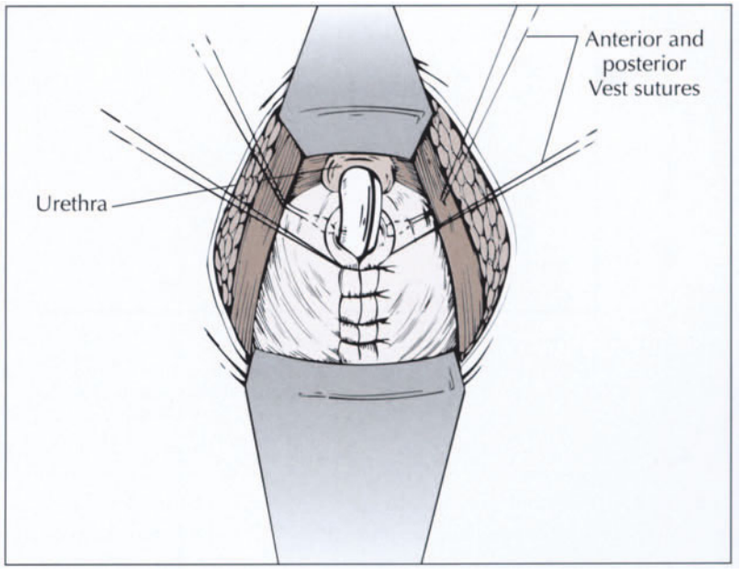


FIGURE 10-19. Anastomosis of bladder neck to urethra. Four bladder neck sutures are left long for Vest sutures. Urethrovesical anastomosis is performed using 2-0 chromic sutures anteriorly, and a 20-F Foley catheter is passed into the bladder. Posterior sutures are then tied, allowing direct visualization of the anastomosis. Vest sutures are passed through the superficial perineal muscles and lightly tied as stay sutures. (*Adapted from* Sullivan *et al.* [13].)

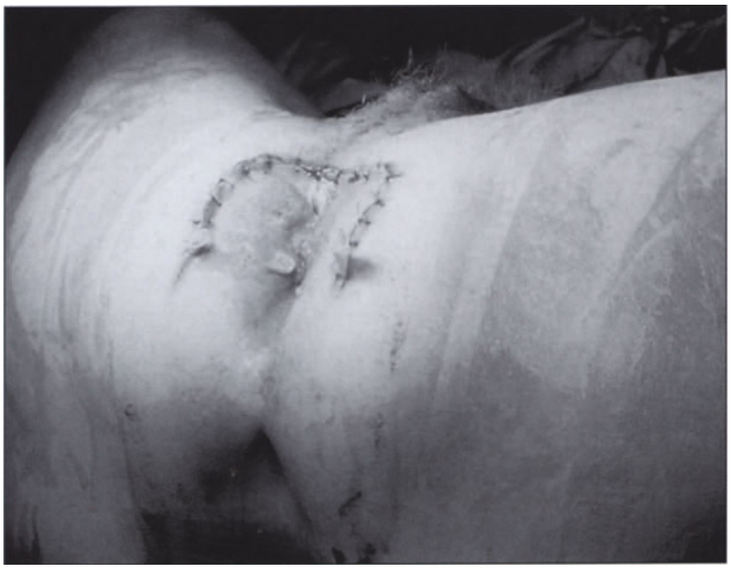


FIGURE 10-20. Closure of central tendon and skin. The central tendon is closed with 2-0 chromic interrupted sutures. Two one-quarter-inch Penrose drains are placed into the ischiorectal fossae, and the skin is then closed with 3-0 chromic sutures. Bupivacaine 1% is injected into the posterior aspect of the wound, and a single 50-mg diclofenac sodium suppository is placed in the rectum. The wound is appropriately dressed.

Incidence of Complications

	*Sullivan et al. [14]**	*Frazier et al. [18]*	*Harris and Thompson [19]*	*Mokulis and Thompson [20]*
Urinary fistula	1 (1.3)	1 (1)	1 (1)	2 (1.7)
Rectal injury	2 (2.5)	NA	NA	12 (10)
Urethral stricture	15 (19)	8 (7)	5 (5)	NA
Wound infection	1 (1.3)	1 (.8)	3 (3)	1 (.8)
Blood transfusions	1 (1.3)	NA	16 (16.7)	6 (5)

**Numbers in columns express number of patients and percentage (in parentheses).*

FIGURE 10-21. Incidence of complications. The perineal approach results in few local complications. Urethral strictures occur in between 5% and 15% of patients and are easily managed with one or two dilations performed in an outpatient or clinic setting. Rectal injury in the University of British Columbia (UBC) series occurred in only two patients: one following previous transurethral resection of the prostate, and one in a patient who underwent salvage prostatectomy [13,15].

The incidence of wound infection and urinary fistulas is low (successfully treated by insertion of a catheter for 10 days [14]). Additional complications occurring in the UBC series at a low incidence rate included perineal hematoma (1.3%), thrombosed external hemorrhoids (1.3%), ileus lasting 7 days (1.3%), and transient hydronephrosis caused by a small ureteral calculus requiring a temporary percutaneous nephrostomy tube. In most series the rate of blood transfusions is low. NA—not applicable.

Rate of Incontinence

Continent: 89% (n = 70/79)
Safety pads or stress incontinence: 8% (n = 7/79)
Severe incontinence (continuous pads): 3% (n = 2/79)

FIGURE 10-22. Rate of incontinence. In the series by Sullivan *et al.* [14], patients were assessed for continence 1 year postoperatively as part of a quality-of-life questionnaire (UCLA/RAND Prostate Cancer Index), which was independently reviewed. Thirty-six of 47 patients who were 1 year postoperative responded. The results were compared with the cohort of retropubic prostatectomy patients who were studied at the same time. There was no significant difference in overall scores between groups (P = 0.79).

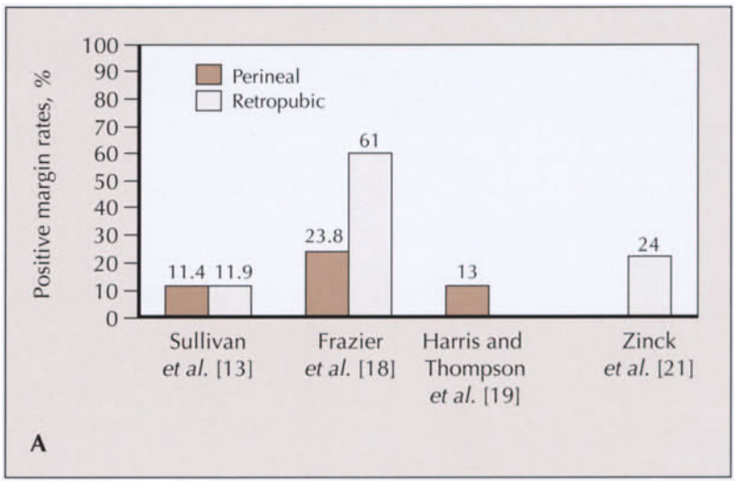
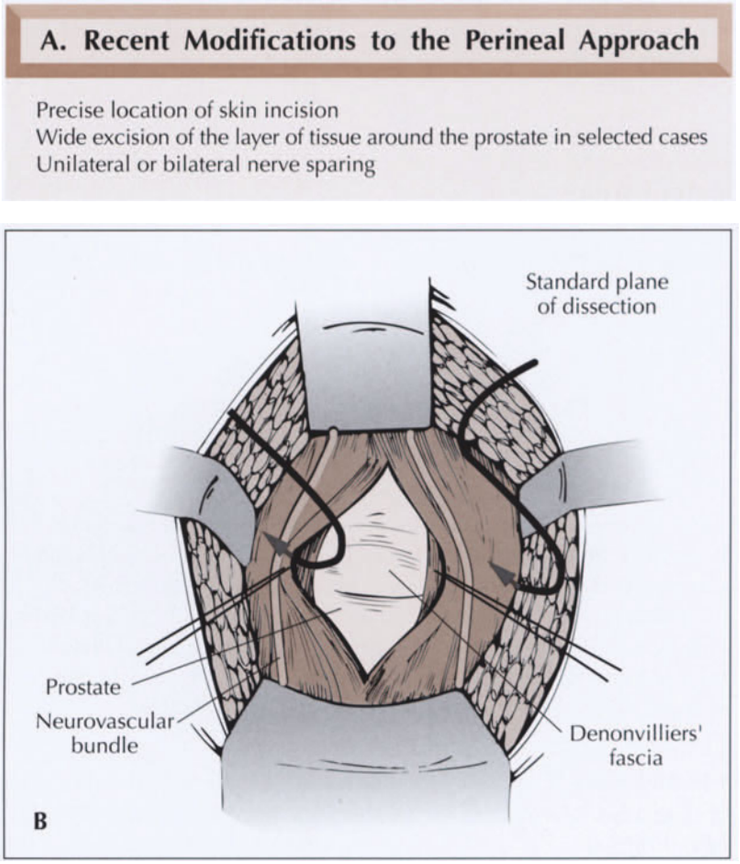


FIGURE 10-23. Cancer control rates. Positive margin rates (**A**) and prostate-specific antigen (PSA) detectability (> 0.2 ng/mL) (**B**) are shown for Sullivan *et al.* [14] and other series [18–22]. At the University of British Columbia (UBC) [14], there was no statistically significant difference in positive margin rates (chi-squared test, $P = 0.9$) or PSA detectability (Kaplan-Meier log-rank test, P = 0.44) between radical perineal and radical retropubic prostatectomy patients. Note that 77.2% of the perineal patients and 71.1% of the retropubic patients in the UBC series were treated with neoadjuvant hormones according to various protocols, which may explain the lower positive margin rates compared with that of other series.



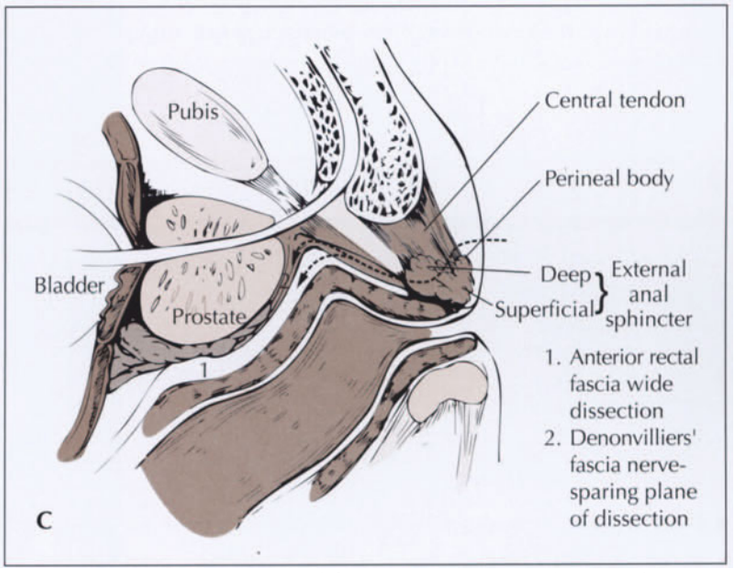


FIGURE 10-24. Recent modifications to the perineal approach. Modifications have been made to the perineal approach to radical prostatectomy since the mid-1990s (**A**). Attempts have been made to ensure a more precise location of the skin incision to position the surgeon reliably in the space between the superficial external sphincter and the longitudinal muscle fibers of the ureter (**B**; see Fig. 10-5).

In addition, attempts have been made to perform a wide excision of the layers of tissue around the prostate in selected cases in which positive margins are a potential concern. This allows the surgeon to remove the Denonvilliers' fascia completely, as well as, in selected cases, a layer of the rectal fascia, one or both of the neurovascular bundles, and some levator tissue en bloc, providing a wide surgical margin (**C**).

A third modification includes unilateral or bilateral nerve sparing, which can be performed as described by Weldon and Tavel [12]. Avoidance of traction on these nerves is essential. (**C** *adapted from* Sullivan *et al.* [13].)

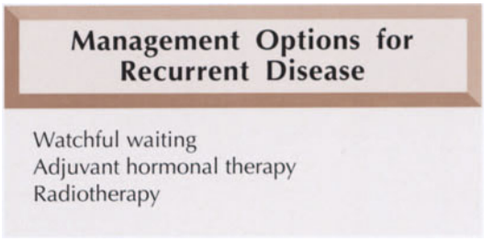


FIGURE 10-25. Management of recurrent disease. Patients should be followed carefully with postoperative prostate-specific antigen (PSA) tests at 3, 6, and 12 months, and then yearly thereafter. Digital rectal examinations should be performed once a year. Patients with a positive PSA test (>0.2 ng/mL) are offered watchful waiting or adjuvant hormonal therapy for a minimum of 6 months. If the PSA level rises again after 6 months of hormonal therapy, patients are offered intermittent hormone therapy [22]. Radiotherapy may be offered if there is positive, biopsy-proven local disease, but only after careful discussion with the patient about the risks related to continence and potency [23].

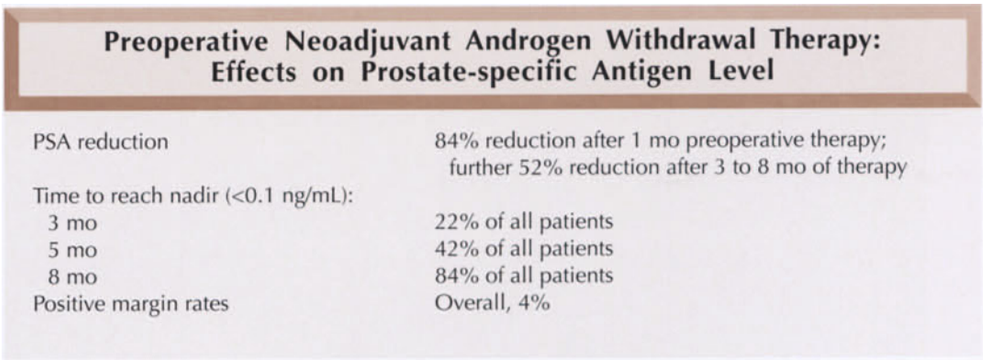


FIGURE 10-26. The effects of 8 months of preoperative neoadjuvant androgen withdrawal therapy before radical prostatectomy [24]. It has been shown that 8 months of neoadjuvant therapy results in low-nadir prostate-specific antigen (PSA) levels preoperatively in the majority of patients, as well as low positive margin rates. The effect on survival remains unknown. It has also been shown, however, that patients with a PSA level of less than 4.0 ng/mL are likely to have organ-confined disease and are unlikely to benefit from preoperative neoadjuvant therapy [25].

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11

Nerve-sparing Radical Retropubic Prostatectomy

David F. Jarrard

The development of the radical prostatectomy over the past 20 years has been marked by an improved ability to extirpate the tumor, combined with a substantially reduced morbidity due to the effects of the operation. A continuum of anatomic discoveries have occurred over the past 30 years pioneered to a significant extent by Walsh [1,2]. These advances in our understanding of the anatomy of the pelvic floor musculature and the nerve and vascular innervation have led to marked improvements in postoperative urinary control and erectile function, two of the more common side effects from this operation. In addition, the greater number of cases being performed by urologic surgeons has contributed to better surgical results overall.

Prostate cancer is the most commonly diagnosed solid tumor, and the second most common cause of cancer death in men in the United States [3]. With the aging population and longer life expectancy, the population at risk is expected to increase. Over half of the men that choose therapy select radical retropubic prostatectomy (RRP) and in general these men are younger and healthier than those who select radiation [4]. RRP can generate excellent cure rates in men with prostate cancer that is confined to the prostate gland or immediate periprostatic tissue. In a large multicenter trial, disease-specific survival rates 10 years following surgery were 94%, 80%, and 77% for those men with low, intermediate, and high-grade tumors, respectively [5]. Often, the efficacy of surgery is based not on patient survival, but on the presence and persistent rise of the serum prostate-specific antigen (PSA) level postoperatively. The PSA level should remain in the undetectable range if all prostatic elements and tumor have been resected. In large studies, the 10-year actuarial likelihood of an undetectable PSA after surgery are 70% to 80% [6,7]. The risk of PSA failure may be predicted from preoperative data for individual patients [8]. In sum, excellent cancer control rates can be obtained in appropriately selected patients.

In this chapter I update a surgical technique for RRP that has been described by Stapleton and Scardino in the first edition of this book [9]. To illustrate both the nerve-sparing and wide excision techniques, the management of a young patient with an intermediate-grade palpable tumor on the right side of the prostate adjacent to the neurovascular bundle is presented.

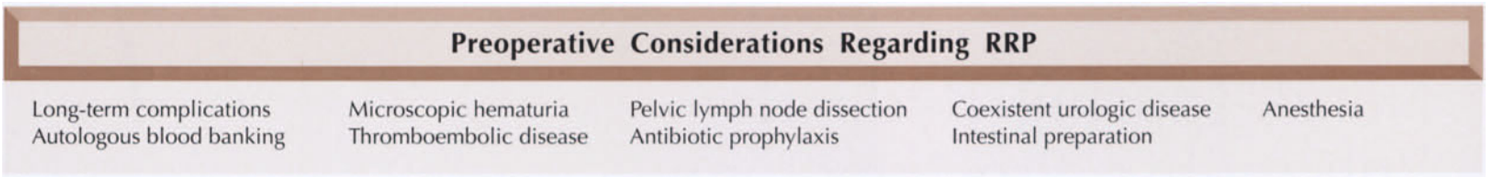

FIGURE 11-1. Indications. Some controversy surrounds the selection of men who might benefit from radical retropubic prostatectomy (RRP) given that there is considerable discordance between those with histologic evidence of prostate cancer and those who develop clinically significant disease [10]. Life expectancy is important to estimate based on age, family longevity, and comorbid diseases. Generally, RRP is a treatment option for men who are expected to live 10 or more years. For example, the average man aged 65, 70, or 75 years with clinically localized prostate cancer of moderate grade treated conservatively can expect to lose 4.5, 4, and 3.3 years of life, respectively [11]. A detailed discussion regarding patient selection can be found in other sources [12–14].

Cancer stage, volume, and preoperative grade have an important impact on the success of RRP in removing the tumor completely. Predictions of postoperative outcomes have been made using preoperative criteria, including grade, clinical stage, and prostate-specific antigen (PSA) level. Both final pathologic outcomes have been estimated using the Partin tables [15], as well as likelihood of PSA failure at 5 years for individual patients [8]. In an analysis of 2402 patients with clinically localized prostate cancer (T1 to 2, NXM0) with intent to treat by RRP, the overall actuarial 5-, 10-, and 15-year recurrence-free survival rates for these men were 84%, 74%, and 66%, respectively [6]. The actuarial likelihood of a postoperative recurrence is elevated with increasing clinical stage, Gleason score, preoperative PSA level, and pathologic stage. Other series have similar findings [7,16,17]. The majority of prostate cancers detected by current diagnostic tests are clinically significant as determined by tumor volume and grade [18–20].

The RRP procedure offers several advantages over the perineal approach, including the opportunity to perform a pelvic lymph node dissection through the same incision. We no longer routinely perform frozen sections unless the nodes are grossly enlarged and highly suspicious for cancer, because the risk of positive nodes is only 2% to 3% in modern series. In addition, recent evidence suggests a therapeutic role for lymph node dissection in selected cases in conjunction with prostatectomy [21]. In this cooperative group study, in patients with minimal nodal disease, pelvic lymph node dissection in combination with radical prostatectomy resulted in freedom from PSA failure at 5 years in 20% of men. However, if multiple grossly involved pelvic lymph nodes are identified, the prostatectomy is typically abandoned, because these patients uniformly fail with distant disease. Other advantages of the retropubic approach include the more familiar anatomy, more consistent success with preservation of the neurovascular bundles, and a greater flexibility to adapt the operation to the extent of each individual's cancer, thus minimizing risks of positive surgical margins. The recent use of laparoscopic radical prostatectomy is based on the retropubic approach, and early indications suggest it may be associated with a more rapid recovery than open surgical approaches [22].

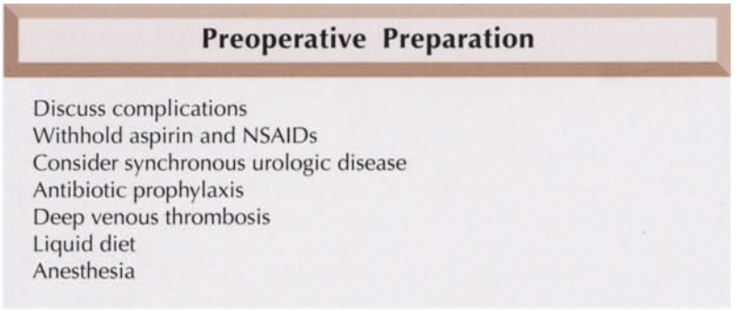

FIGURE 11-2. Preoperative preparation. Complications of radical retropubic prostatectomy (RRP) that need to be addressed with the patient during the informed consent procedure include urinary incontinence, erectile dysfunction, bleeding, infection, bladder neck stricture, and other rare major morbidities, including heart attack and stroke. These are discussed in more detail in the last section of this chapter. A careful medical history and physical examination are required to exclude major comorbidities. A bone scan and CT scan are generally not performed for patients with prostate-specific antigen (PSA) levels less than 20 ng/mL or a Gleason sum of 6 or less because the positive yield is 2% and 9%, respectively, in this group [23]. The positive yield is higher for individuals having both a Gleason sum of 7 or greater and a PSA higher than 10 ng/mL or for individuals having Gleason scores greater than 8.

Intraoperative blood loss during RRP has been substantially reduced, largely because of the improved understanding of dorsal vein anatomy and subsequent refinements of operative technique [1]. Intraoperative blood loss is on average less than 1 L [16,24,25]. Transfusion rates vary from 10% to 30% [24,25]. A cost-benefit analysis indicates that in many cases, autologous blood donation cannot be supported; however, risk assessment should be left up to the individual patient [24,25].

Aspirin and NSAIDs should be withheld for 10 days prior to surgery because they impair platelet function. These medications can be safely restarted in the early (1- to 2-week) postoperative period.

The presence of synchronous urologic disease needs careful preoperative evaluation. Microscopic or gross hematuria, sometimes associated with prostate cancer, should be evaluated with cystoscopy and intravenous pyelogram preoperatively. Preoperative incontinence or other bladder dysfunction needs further evaluation, including urodynamics. A history of prior transurethral prostatic surgery is associated with diminished post-RRP urinary control, as are symptoms of bladder dysfunction such as urge incontinence [26]. The risks associated with these conditions need to be discussed with the patient preoperatively.

The use of antibiotic prophylaxis is recommended for RRP, a clean-contaminated procedure. The initial dose of a broad-spectrum antibiotic (*eg*, second- or third-generation cephalosporin) with activity against common skin and uropathogens should be given intravenously prior to the induction of anesthesia to achieve a satisfactory serum level at the time of incision.

Deep venous thrombosis and pulmonary embolism associated with RRP occurs in about 1.1% and 1.3% of patients [24]. Controversy exists surrounding the use of anticoagulants and compression stockings. The use of compression devices to the lower limbs intraoperatively has not demonstrably lowered the clinical detection of thromboembolic events and may lead to increased blood loss [27]. Subcutaneous low-dose heparin may decrease thromboembolic events; however, it appears to increase bleeding and lymphocele formation [28]. Low molecular weight heparin appears to be effective at preventing deep vein thromboses and may avoid these other side effects, although this has not been tested specifically in RRP. Dorsiflexion exercises of the lower limb and early ambulation are important postoperatively.

A liquid diet is recommended for the 24 hours prior to surgery, and the lower bowel is prepared with a phosphate enema on the morning of surgery.

Either general anesthesia with muscle relaxation or epidural with sedation allows for adequate pelvic exposure. The preoperative placement of an epidural catheter for supplementary anesthesia allows intraoperatively controlled hypotension that can reduce blood loss, and also allows highly effective postoperative pain management [29]. This catheter is typically withdrawn on or before postoperative day 2.

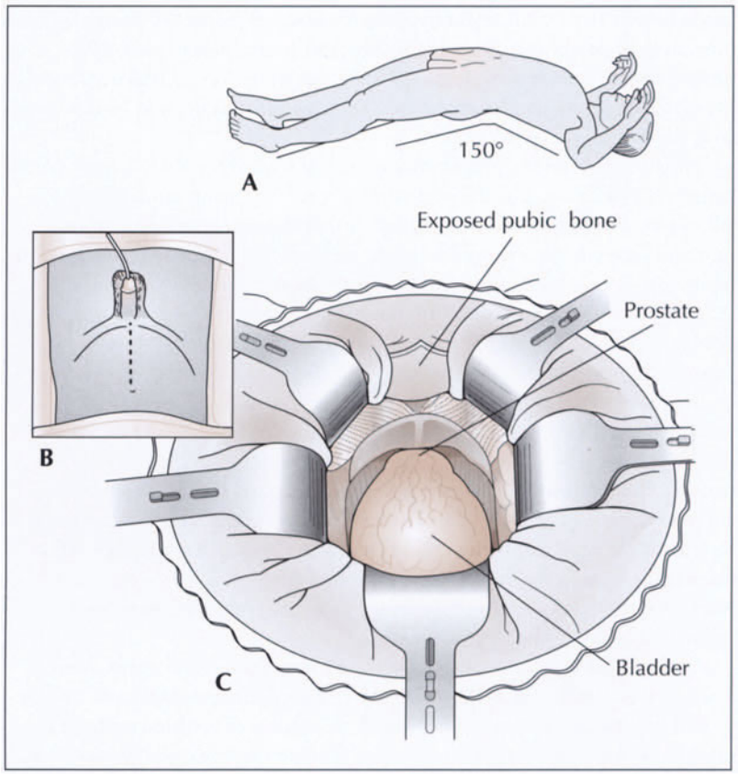

FIGURE 11-3. Patient positioning. The patient is positioned supine with the table maximally flexed (**A**). The arms are abducted and externally rotated with the elbows flexed at 90°, and the wrists fixed to a frame that is positioned across the head of the patient. Through a suprapubic midline incision that reaches toward the umbilicus (**B**), the transversalis fascia is incised sharply and the retropubic space entered. Care is taken not to sweep perivesical lymph nodes cephalad as the lateral pelvic walls are exposed back to the level of the obliterated umbilical arteries. A Turner Warwick self-retaining retractor (**C**) is a satisfactory device to provide adequate pelvic exposure, or alternatively a Balfour retractor with a right-angle blade may be utilized. Occasionally, a bony spur protruding from behind the symphysis pubis will compromise the view of the prostatic apex. This can be removed using an osteotome and mallet. An 18-F Foley catheter is inserted and 25 cc of fluid placed in the balloon.

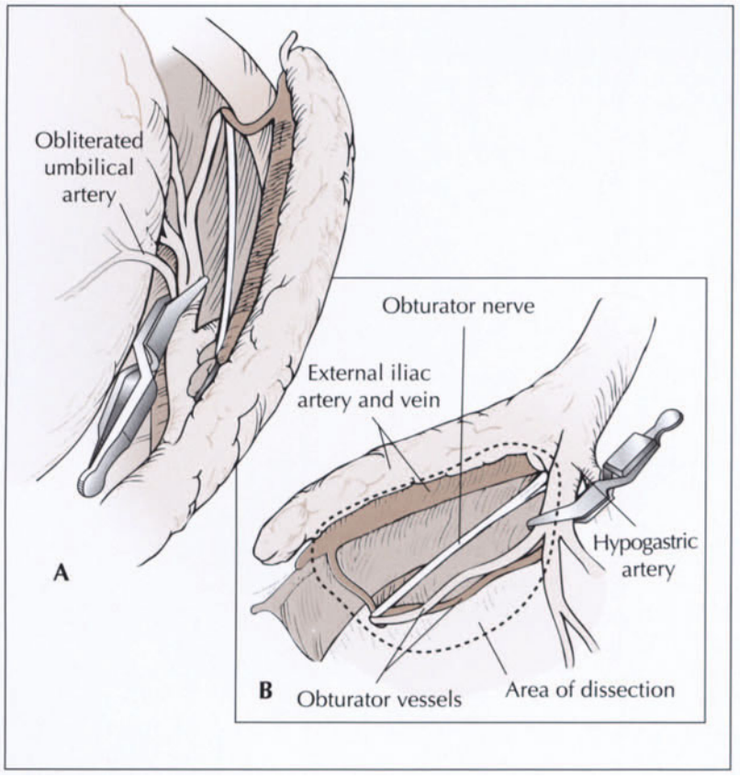

FIGURE 11-4. The anatomic structures relevant to the pelvic lymph node dissection. A bilateral pelvic lymph node dissection is performed using the external iliac vein as the superior margin, the obturator nerve as the inferior margin, the obturator canal caudally, and the bifurcation of the common iliac cranially. **A,** The nodal dissection is begun on the ipsilateral side of the prostate containing the major tumor. Lymphatic channels are carefully clipped. **B,** To reduce intraoperative blood loss, bulldog clamps may be placed across the hypogastric arteries just distal to the obliterated umbilical artery. Such application may reduce intraoperative bleeding, and placement generally is made without difficulty.

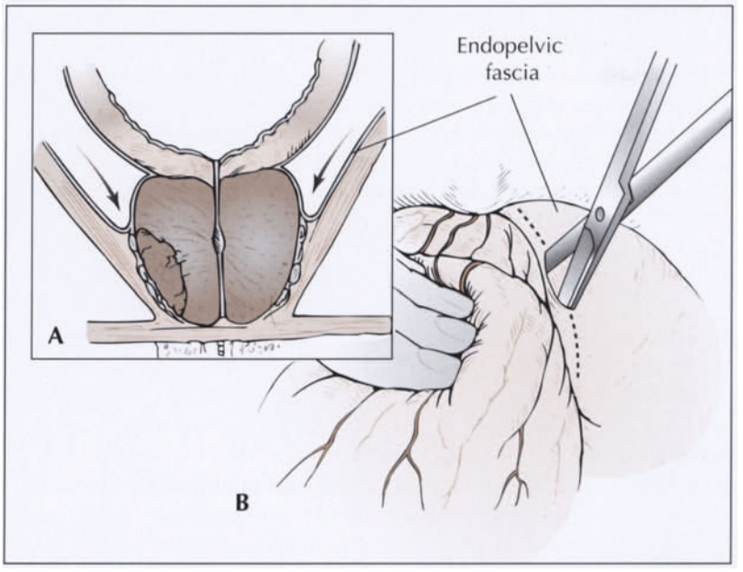

FIGURE 11-5. Perforating the endopelvic fascia. The loose fatty tissue behind the symphysis pubis is gently teased out using nontoothed forceps to expose the superficial dorsal venous plexus. The prostate is then mobilized by dividing the endopelvic fascia laterally (**A**), initially by puncturing with closed scissors into the deep natural groove between the prostate and the pelvic side wall (**B**). Care must be taken to avoid the venous plexus on the surface of the prostate.

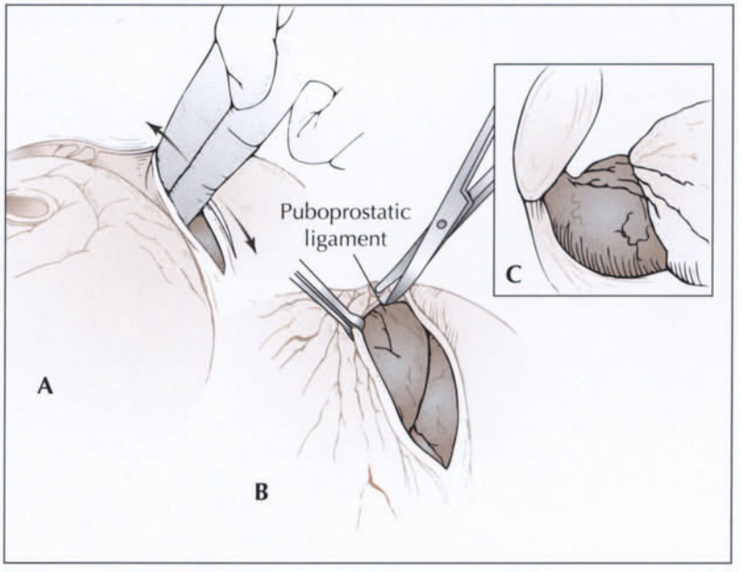

FIGURE 11-6. Division of the endopelvic fascia in an anterior and posterior direction using both blunt finger (**A**) and sharp (**B**) dissection. Careful dissection with a Kitner (peanut) dissector (**C**) near the apex of the prostate can help delineate small branching vessels from the levator muscles that can be controlled with clips prior to the complete division of the puboprostatic ligaments. The puboprostatic ligaments are then divided with scissors close to their bony origins. The prostate is then carefully palpated for induration. This information, combined with preoperative information regarding the location of the cancer, will determine the feasibility and safety of a nerve-sparing procedure.

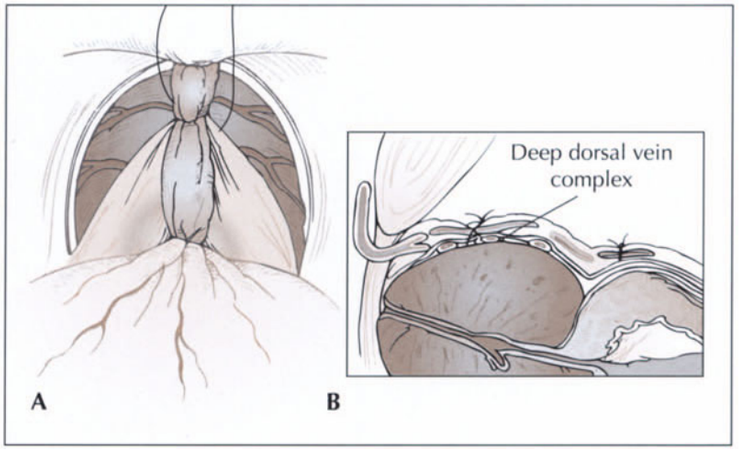

FIGURE 11-7. Suture placement. The superficial dorsal venous complex is controlled with a suture approximately 1 cm cephalad to the bladder neck, which is determined by its relationship to the catheter balloon. This stitch serves to limit back bleeding and also marks the anterior limit of the proximal dissection at the bladder neck during the final stages of the removal of the prostate (**A**). The incised endopelvic fascia and deep dorsal vein complex are gathered in a figure-of-eight suture placed anteriorly over the apical half of the prostate (**B**). This suture is tagged with a hemostat and used as countertraction to aid in gentle finger dissection of the dorsal venous complex and identification of the urethra distal to the apex of the prostate (see Fig. 11-8).

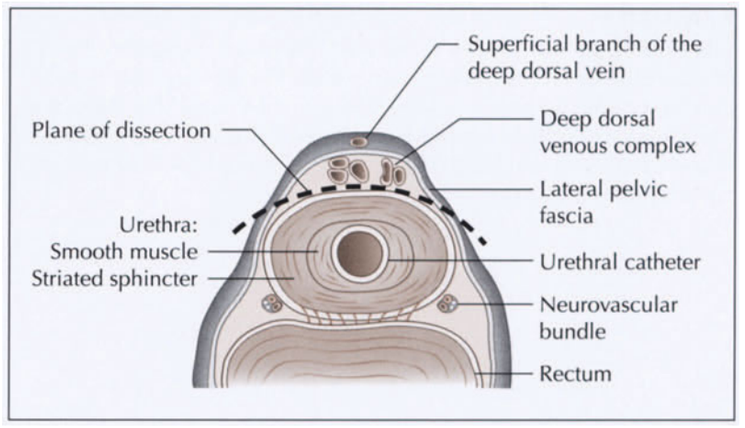

FIGURE 11-8. The proximal urethra and dorsal venous complex. Correct identification of the urethra and the avascular plane that runs below the dorsal venous complex is critical. A finger is used to palpate and identify the avascular plane superior to the urethra and below the dorsal vein complex. The Foley catheter serves as a guide. The apex and anterior surface of the prostate must be carefully avoided.

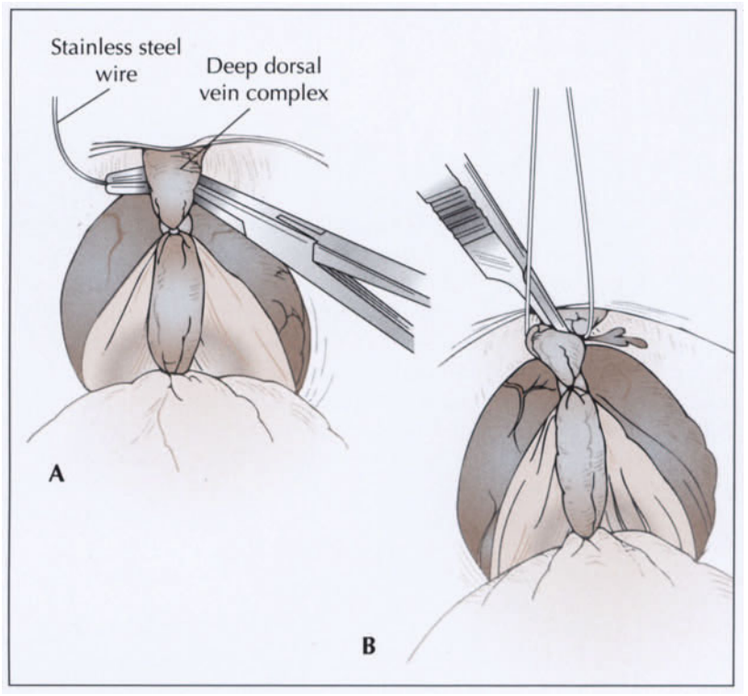

FIGURE 11-9. Once the plane of dissection is identified, a long-tipped, right-angled clamp is passed immediately superior to the urethra, below the dorsal vein complex, in the avascular plane. A steel wire can be used to isolate the dorsal venous complex (**A**). With upward retraction on the wire and the prostate firmly pushed down with a sponge stick, the deep dorsal venous complex is sharply divided with a number 15 blade (**B**).

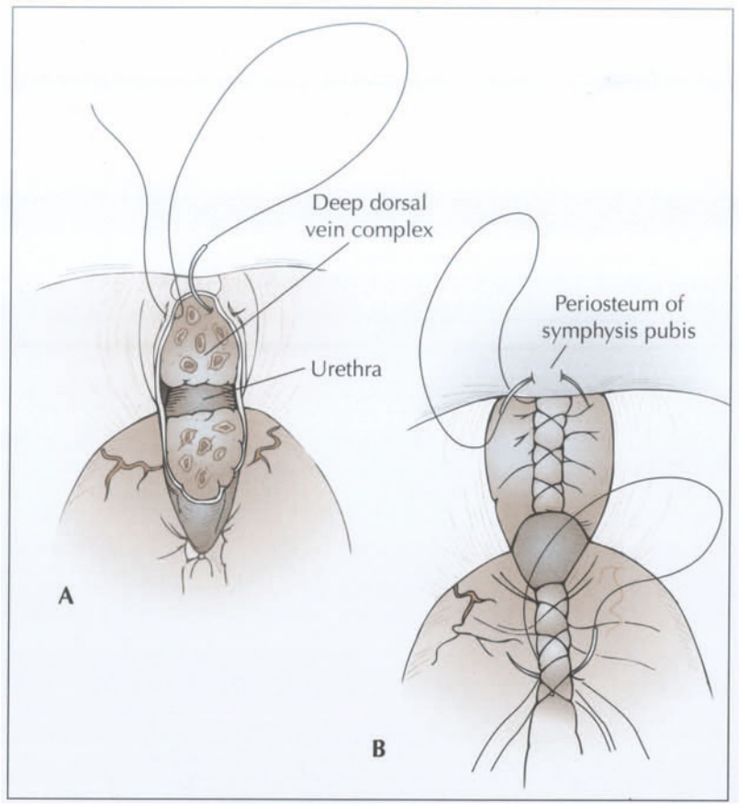

FIGURE 11-10. Control of bleeding. With the surgeon standing adjacent to the patient's left thigh and facing cephalad, the dorsal venous complex is brought under control through apposition of the lateral pelvic fascia using a continuous vertical absorbable suture (**A**). The last pass is brought through the periosteum of the pubis (**B**) to effectively compress the superficial dorsal veins in the anteroposterior plane and to fix the fascia to the periosteum, simulating the function of the puboprostatic ligaments. Back bleeding from the ventral prostate is controlled with a continuous hemostatic suture (**B**).

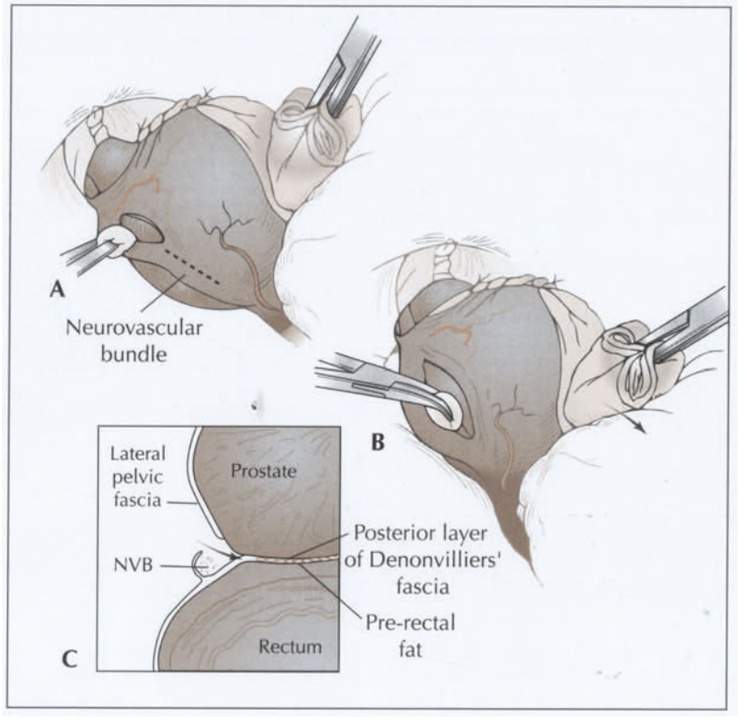

FIGURE 11-11. Examination of each neurovascular bundle (NVB). By rotating the prostate laterally with a sponge stick, the surgeon can examine the course of the NVBs in relation to the prostate and to any palpable tumor. Frequently, a shallow groove defines the superior margin of dissection for the preservation of each bundle. A plane of division of the lateral pelvic fascia is then chosen to assure a negative surgical margin while as much of the NVB and its fibers are preserved as possible. Once the level of dissection is determined, the lateral pelvic fascia is sharply incised from the base of the prostate toward the apex using a right angle and scissors (**A**). Muscle bundles of the levator ani are then further stripped away from the apex of the prostate using scissors or bluntly with a peanut dissector to expose the prostatourethral region posterolaterally (**B** and **C**). The NVB is then gently dissected and displaced laterally working from the apex toward the base. Small arterial and venous branches are clipped and divided. Care must be taken to avoid electrocautery near this neural tissue. *Note*: This apical neural dissection may be performed after transection of the urethra as described by Walsh.

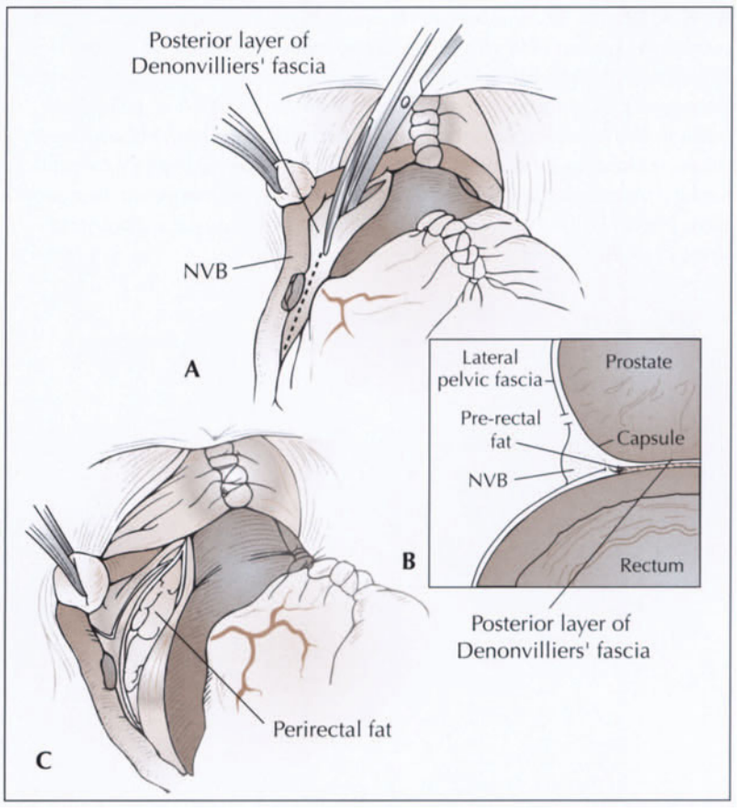

FIGURE 11-12. Division of posterior layer of Denonvilliers' fascia. This layer can be punctured with closed scissors immediately lateral to the prostatourethral junction to expose perirectal fat. The plane of dissection is then developed using both a peanut dissector and scissors (**A–C**). Special attention is paid to continuing the posterolateral displacement of the neurovascular bundle (NVB) away from the urethra for a distance of almost 1 cm from the prostatourethral junction to lessen its risk of entrapment when the vesicourethral anastomosis is completed. If the tumor is palpably close to a neurovascular bundle (see Fig. 11-13), then the dissection is started further posterolaterally to include the bundles with the pathologic specimen.

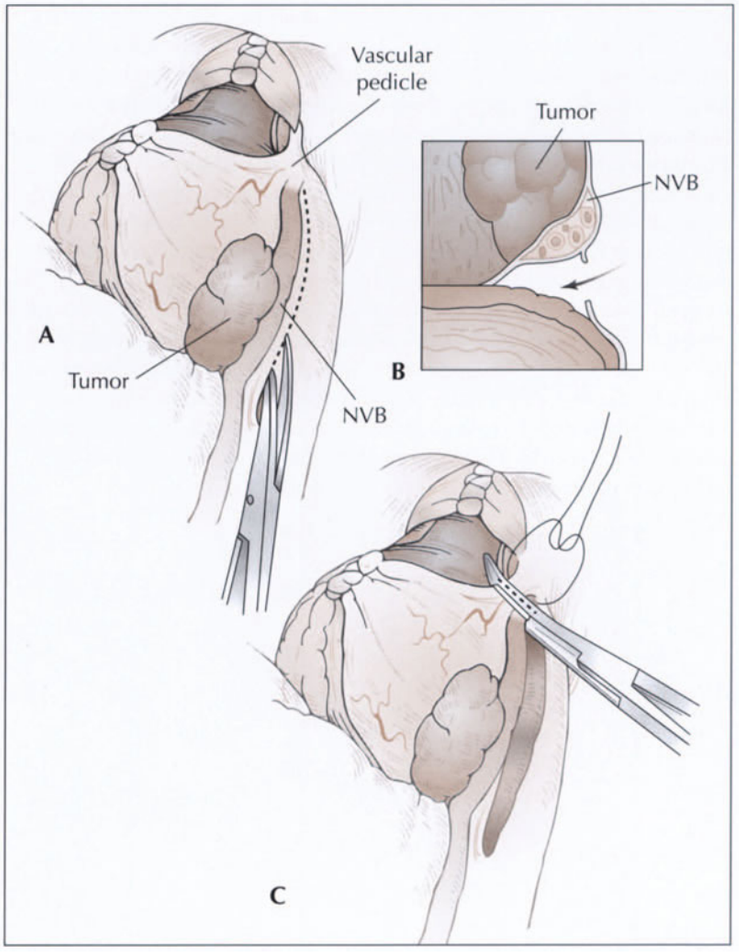

FIGURE 11-13. Resection of one neurovascular bundle (NVB). Should the cancer lie close to an NVB, all or part of the bundle should be resected to assure a negative surgical margin. A plane of dissection is chosen laterally. If the entire bundle is to be resected, dissection begins over the lateral rectal wall, in the fat plane beneath the NVB (**A** and **B**). The incision is extended distally and the NVB is secured with clips or ties and divided distal to the apex of the prostate (**C**).

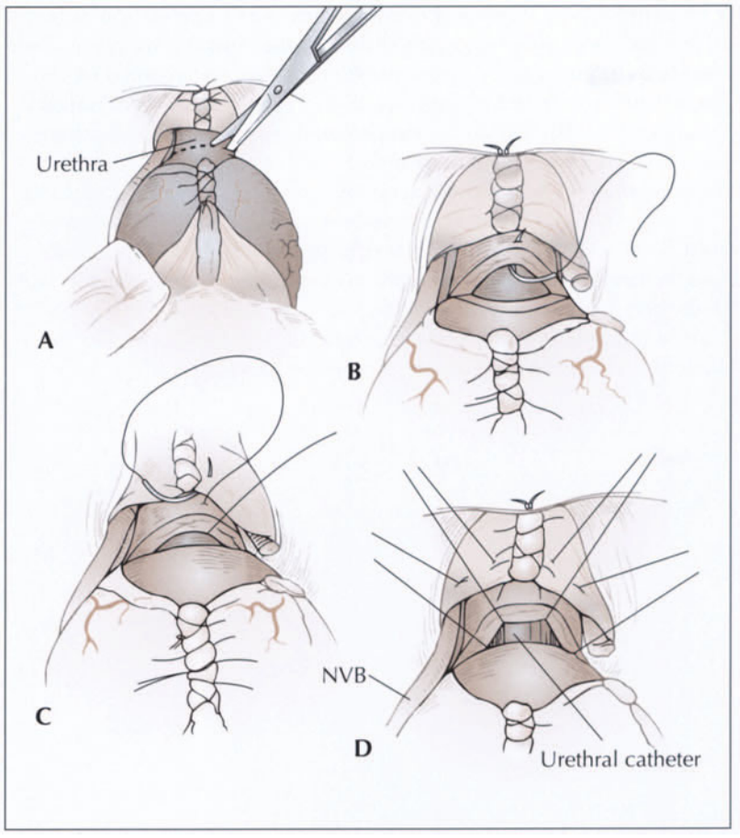

FIGURE 11-14. Division of anterolateral urethra and placement of anastomotic sutures. The anterolateral urethra is divided 2 to 3 mm from the apex of the prostate (**A**) and a total of four to six 3-0 monocryl sutures are placed at regular intervals around the urethra starting at 12 o'clock. Each suture includes urethral mucosa (**B**) and, in a separate bite, a firm piece of lateral pelvic fascia (**C** and **D**). Additional security for each of these anterior sutures is obtained by gathering a separate bite of several millimeters of the lateral pelvic fascia that had been sutured earlier to control the divided deep dorsal venous complex. The catheter is then pulled back to expose the entire urethra. Care is taken to ensure that the posterior apical prostatic tissue, often seen as a lip extending further posteriorly than its anterior counterpart, is fully resected with the specimen by careful blunt dissection with the peanut dissector.

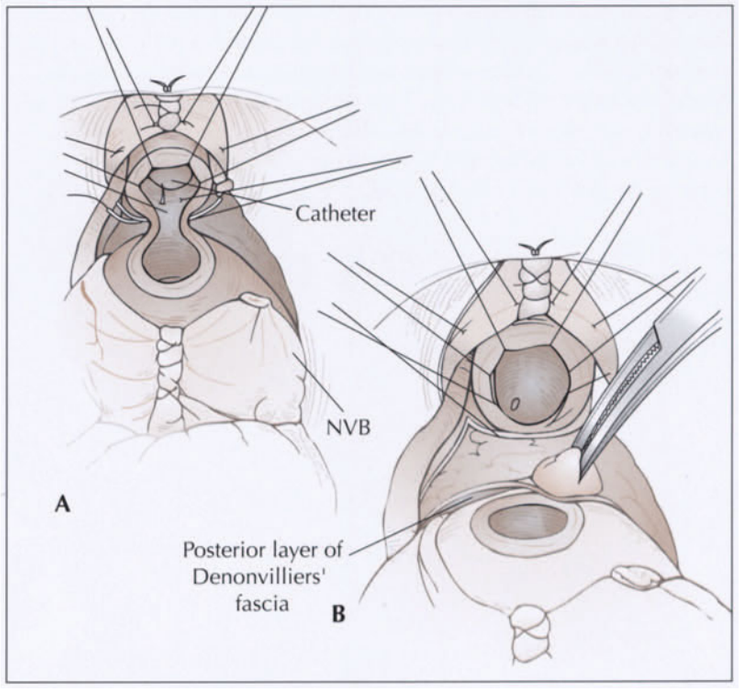

FIGURE 11-15. Completion of urethral division. Two or three posterior anastomotic sutures are placed to include the posterior layer of Denonvilliers' fascia (**A**). The needle on each of these sutures is left on as a marking tag; the anterior sutures will be sewn to the reconstructed bladder neck using a Mayo needle. The urethral division is completed and the incision is carried through the rectourethralis muscle to the fatty tissue anterior to the rectum. By dividing the posterior layer of Denonvilliers' fascia at the apex, the yellowish perirectal fat becomes visible and the correct plane of dissection can be confirmed (**B**). Sharp and blunt dissection is used to elevate the prostate. It is critical to include the shiny posterior layer of Denonvilliers' fascia to reduce the likelihood of a positive surgical margin.

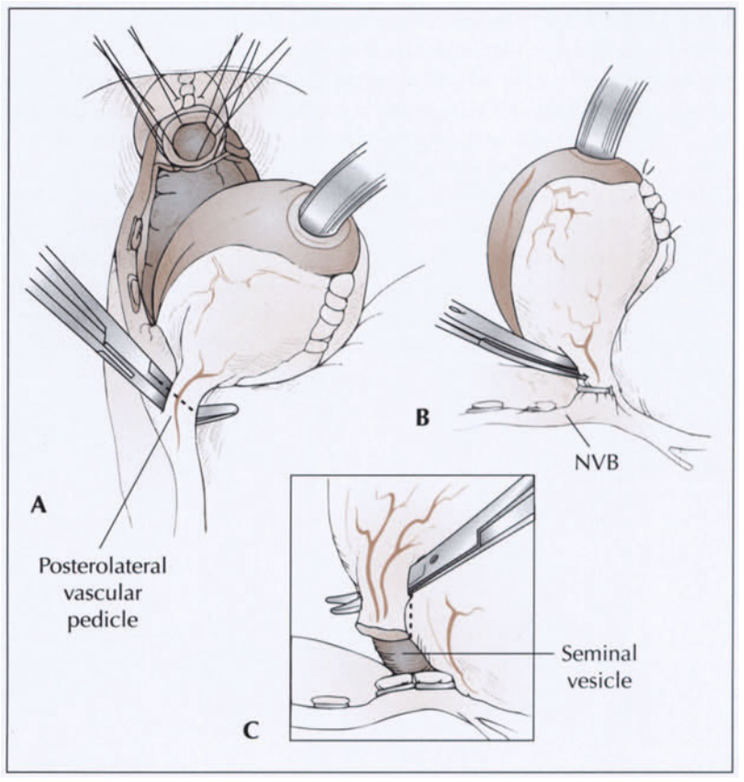

FIGURE 11-16. Mobilization of the prostate. A new catheter is placed in the bladder to allow easy manipulation of the prostate, which is mobilized from its posterolateral attachments in a side-to-side fashion (**A**). Small vessels are controlled with clips placed parallel to the neurovascular bundle (NVB) (**B**). The posterolateral vascular pedicles of the prostate are identified with the aid of a right-angled clamp working in an up-and-down motion to separate tissue appropriate for clip ligation and division. The surgeon needs to remain cognizant of the location of the neurovascular bundles during this dissection because they can be tented up and into the field of dissection secondary to ventral retraction on the prostate. In the posterior midline, the superficial layer of Denonvilliers' fascia is divided transversely at the level of the base of the prostate, entering the plane between the rectum and the seminal vesicles (**C**).

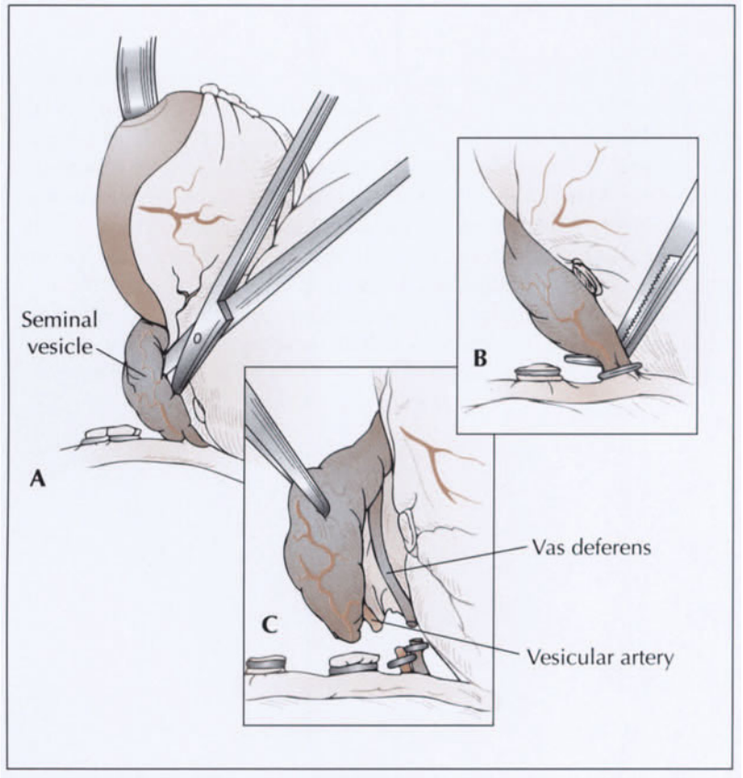

FIGURE 11-17. Approach to the seminal vesicles. The seminal vesicles are typically approached laterally and the plane between the seminal vesicles and the bladder developed with scissors and finger dissection (**A**). The major vascular supply to the seminal vesicles at this point lies anterior and lateral. When these are clipped and divided close to the wall of the vesicle, it is easier to identify the large artery that enters at the apex of the seminal vesicle (**B**). The ampullae of the vasa are clipped to include the vasal arteries, and divided (**C**). The rectovesical fascia should be left covering the resected seminal vesicles.

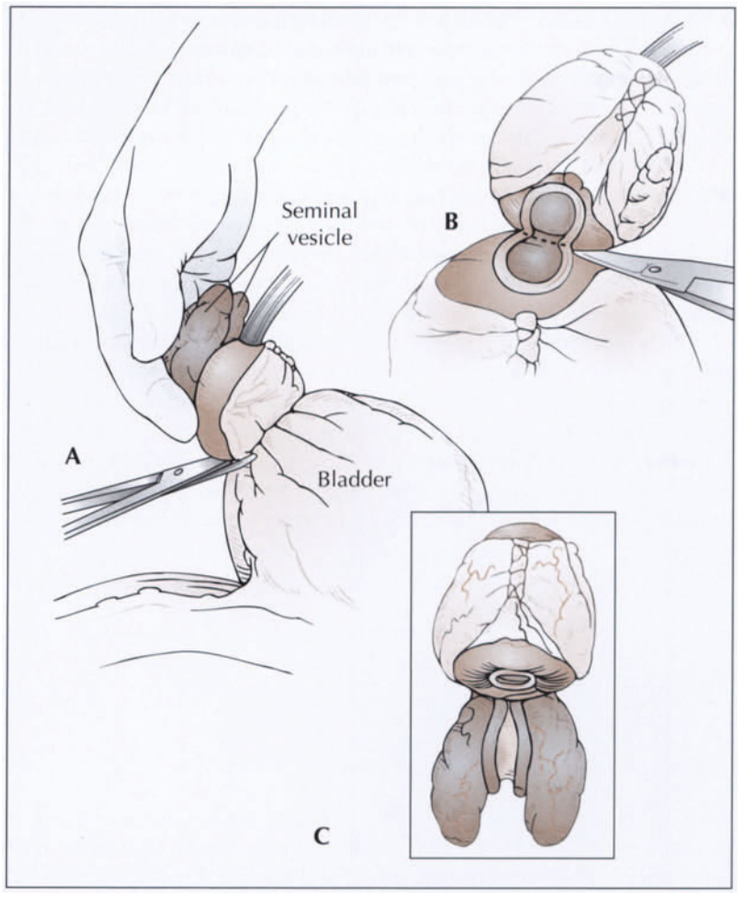

FIGURE 11-18. Division of the bladder neck. The seminal vesicles and vasa are sharply dissected off of the posterior wall of the bladder, staying close to the seminal vesicles. The small vessels from the bladder pedicles are controlled with clips or electrocautery (**A**). The bladder neck is then divided anteriorly, and the catheter balloon is removed through this incision (**B**). Care is taken to preserve as much bladder mucosa as practical, but not to leave behind prostatic tissue. The ureteral orifices are inspected for spontaneous efflux of urine prior to the complete removal of the specimen. An ampule of indigo carmine may be given intravenously to help visualize the ureteral orifices.

C, The posterior bladder neck is then divided under direct vision once the location of the trigone and ureteral orifices has been identified.

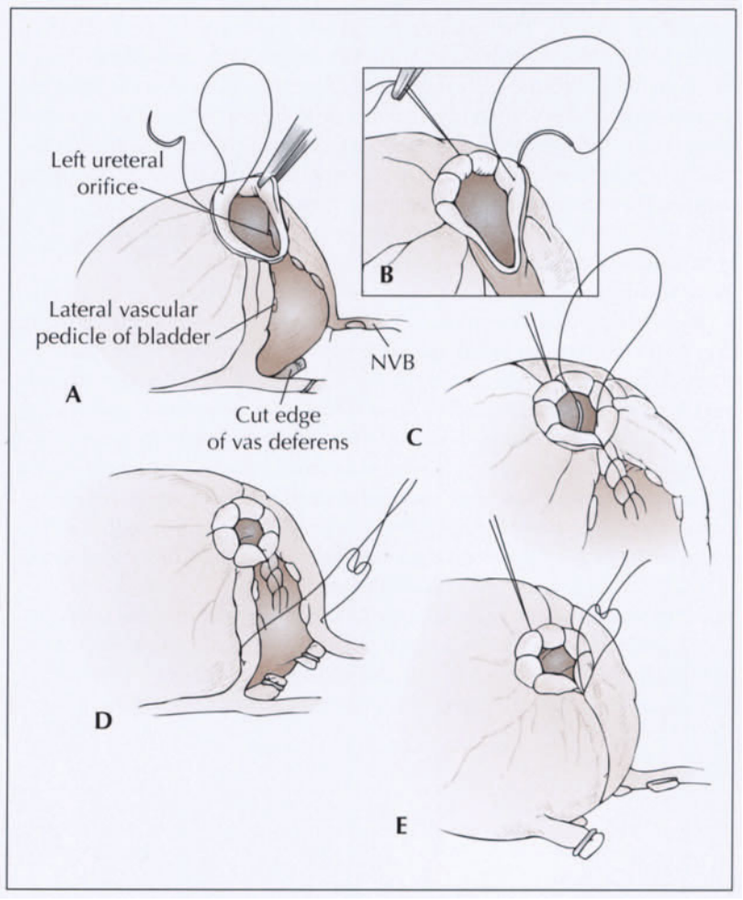

FIGURE 11-19. Preparation of anterior bladder neck for anastomosis. The anterior bladder neck is prepared for the anastomosis by fully everting the mucosa anterolaterally with five 4-0 absorbable vertical mattress sutures (**A** and **B**). The posterior bladder neck is closed in a "tennis racket" fashion with a continuous suture beginning at 6 o'clock and ending with a stitch that fully everts the bladder mucosa (**C** and **D**) providing an opening 8 to 10 mm (24 to 30 F) in diameter. The lateral vascular pedicles of the bladder may be reapproximated with a continuous suture (**D** and **E**) to secure hemostasis if necessary. The operative field is irrigated with 2 L of warmed sterile water. The exact size of the bladder neck is not critical to the attainment of postoperative continence. NVB—neurovascular bundle.

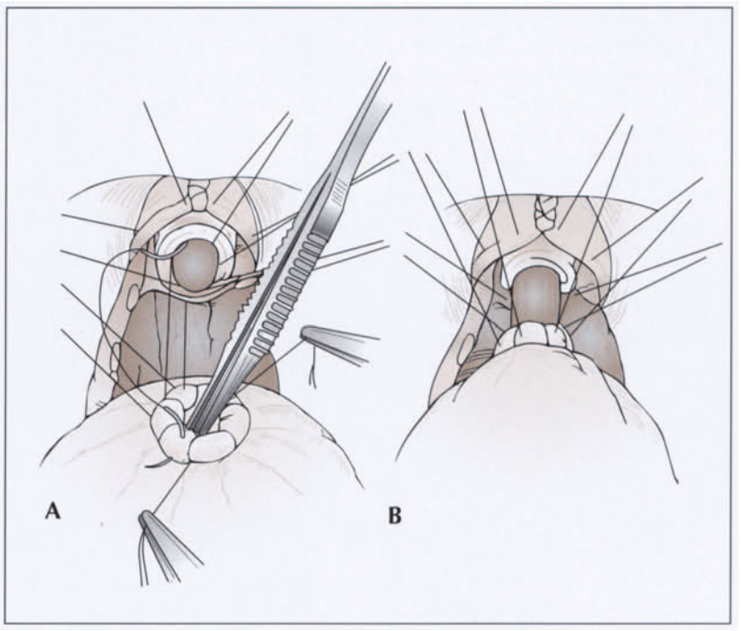

FIGURE 11-20. The anastomotic sutures previously placed in the urethra are positioned appropriately in the bladder neck with the needle entering and exiting through everted mucosa to place the knots on the outside (**A**). The urethral catheter is placed in the bladder and the anterior anastomotic sutures are secured before the catheter balloon is inflated with 15 cc. The operating table is taken out of the flex position to facilitate the advancement of the reconstructed bladder neck to the urethra. Firm traction on all six anastomotic sutures and on the catheter is important to facilitate apposition of the bladder neck to the urethra (**B**). As the sutures are tied, care is taken to exclude the preserved neurovascular bundles by gentle downward pressure applied with a sponge stick.

The bladder catheter is gently irrigated to provide a clear return and test the anastomosis for frank leakage. It is subsequently secured to the thigh without traction. Suction catheters are placed in each obturator fossa, and these are typically removed by postoperative day 2. The average hospital stay is 2 to 3 days. Patients are discharged on oral pain medication and a stool softener. The patients are brought to the office for catheter removal, without a prior cystogram, 10 to 14 days after the operation.

COMPLICATIONS

Complications

Early complications
- Severe blood loss
- Rectal injury (< 1%)
- Operative mortality (0.3%)
- Deep venous thrombosis (1.1%)
- Pulmonary embolism (1.3%)
- Wound infection (1.5%)
- Lymphocele (3.4%)
- Prolonged fluid intake (0.6%)

Late complications
- Anastomotic stricture
- Urinary incontinence
- Persistent erectile dysfunction

FIGURE 11-21. Early and late complications. The estimated blood loss during radical prostatectomy from several large series ranges from 600 to 1400 mL [24]. As noted previously, autologous units may be used if the patients provide these preoperatively; however, they are generally needed in a minority of patients. Other intraoperative complications occur less frequently in the modern era including rectal injury (< 1%), operative mortality (0.3%), deep venous thrombosis (1.1%), pulmonary embolism (1.3%), wound infection (1.5%), lymphocele (3.4%), and prolonged fluid leak (0.6%) [30–32].

Late complications include the incidence of anastomotic stricture, previously a troublesome complication, which has clearly been reduced as a result of vigorous bladder mucosal eversion and a water-tight mucosa-to-mucosa vesicourethral anastomosis. Risk factors for strictures include previous transurethral resection of the prostate, excessive blood loss, and urinary extravasation [33]. The onset of symptoms related to stricture typically occur in the first 12 months after the operation. Rates in modern series range from 3% to 9% [30–32]. Typically these respond well to simple dilation, although occasional strictures require cold knife incision or periodic dilation. The incidence of urinary incontinence varies widely dependent on the population queried, the era of the operation, the questionnaire used, and the strict definition of incontinence. Rates in Medicare patients operated on in the late 1980s were as high as 31% [34]; however, more recent data gleaned from large centers places the rate less than 10% [26,35]. Improvements in incontinence may occur up to 2 years following surgery. Patients receive advice regarding Kegel exercises. Although certainly it is our experience that these exercises are helpful in aiding timely urinary control, definitive proof of benefit has not been obtained.

Risk factors for persistent erectile dysfunction include increasing patient age, status of erections before the operation, the pathologic stage, and degree of resection of the neurovascular bundles [36,37]. Potency rates also vary between centers of excellence (> 60%) and in population surveys (< 30%) [34,38,39]. Because there is often considerable delay in the return of postoperative potency, a penile prosthesis should not be considered before 2 years has elapsed. Rarely are there contraindications to the use of intracavernosal injection therapy or vacuum devices for the treatment of impotence in the early postoperative period (typically 6 weeks or longer postoperatively). Oral therapy with sildenafil (Viagra; Pfizer, New York, NY), a selective phosphodiesterase inhibitor, has been very effective for restoring potency unless both neurovascular bundles are resected [40]. Other oral agents using different mechanisms, such as apomorphine or piperazine analogues, will offer patients other options for inducing erections in the future.

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12

External Beam Radiotherapy for Prostate Cancer

Edgar Ben-Josef & Arthur T. Porter

Controversies in the management of prostate cancer make treatment selection one of the most challenging areas in contemporary oncology. External beam radiotherapy (EBRT) is the one treatment modality that has applications at every stage in the natural history of carcinoma of the prostate. In early disease, it is a curative therapy that can eradicate organ-confined tumor with maximal preservation of adjacent normal tissues. Its efficacy is similar to that of surgery and its side effect profile is favorable. In the past few years, we have seen major advances in the technique of dose delivery. Three-dimensional conformal planning has become widespread and has been proven to allow safe escalation of the radiation dose and to increase disease control [1–5]. Intensity modulated radiotherapy, an advanced form of three-dimensional planning currently under study, holds promise to further improve dose distribution. Another area of intense investigation has been the use of interstitial radioactive implants, alone or in combination with EBRT. In locally advanced prostate cancer (tumor with extension beyond the confines of the glandular capsule, into the seminal vesicles, or into regional structures), EBRT combined with androgen deprivation has become the standard of care [6–9]. For those patients who have undergone surgical resection as the primary form of management, retrospective studies have identified a role for adjuvant EBRT; it provides improved local control for tumors with poor pathologic features (*eg*, positive margins, high grade, advanced pathologic tumor stage) [10–17]. Randomized studies looking at the impact of this treatment on overall survival have now been completed; the results are awaited. EBRT also has a role in salvage therapy for patients with late local recurrences following surgery, whether detected on biochemical studies or by physical examination [14,18–21]. Finally, EBRT has a well-established role in the management of symptomatic osseous metastases, and it generally provides quick and effective pain control.

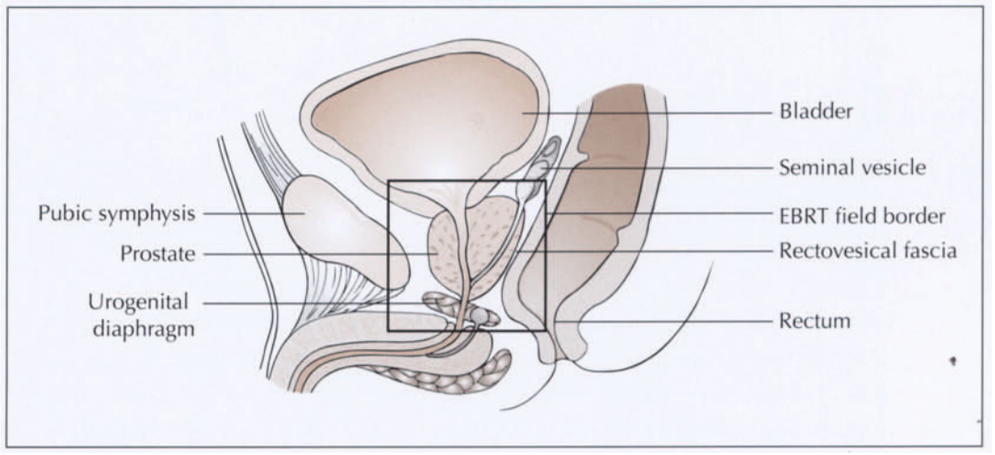


FIGURE 12-1. Sagittal view of the pelvis illustrating the anatomic relationships of the prostate to regional structures. Conventional lateral field borders for treatment of early-stage prostate disease are shown. As illustrated, the prostate lies at the base of the urinary bladder, encompasses the male urethra, and rests on the urogenital diaphragm. Important anatomic relationships that come into consideration when planning external beam radiotherapy (EBRT) to the prostate include 1) the gland's proximity to the rectum, from which it is separated by the rectovesical septum (Denonvilliers' fascia); 2) the size and orientation of the seminal vesicles with respect to the gland (typically, they pierce the posterosuperior aspect of the gland); 3) the relationship to the bladder neck; and 4) the relationship to the pubic symphysis. The understanding of local anatomy helps delineate the boundaries of the prostate because the gland cannot be visualized by conventional radiography.

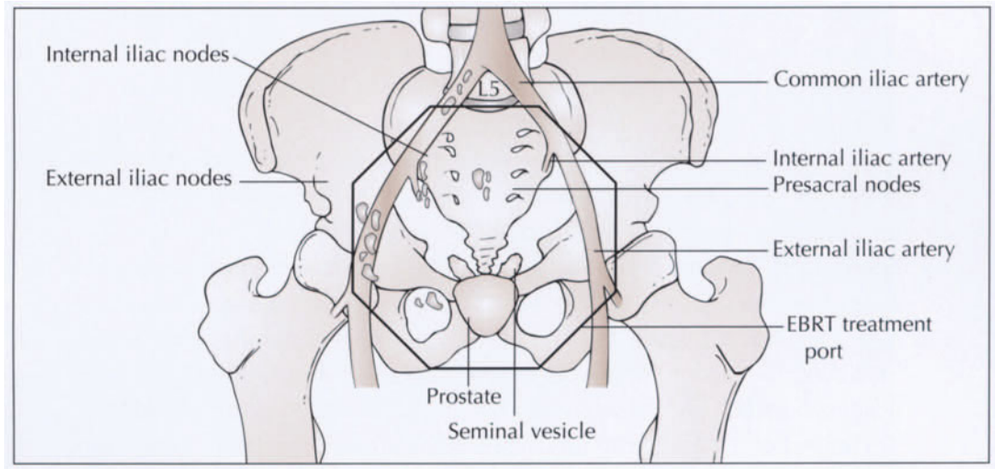
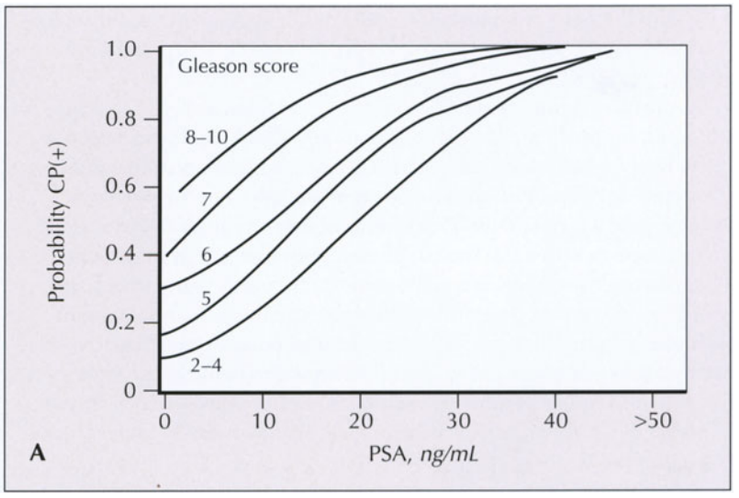
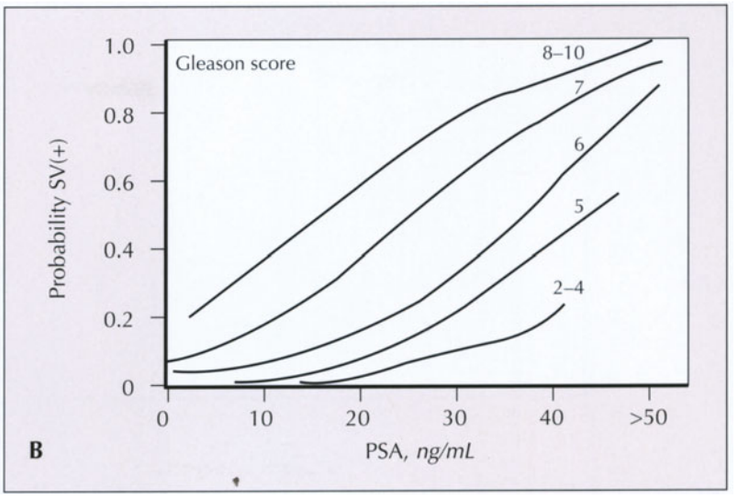


FIGURE 12-2. Anterior view of the pelvis illustrating the lymphatic drainage of the prostate. The outline of a conventional anteroposterior field is shown. Adenocarcinoma of the prostate metastasizes in a fairly predictable pattern. First to be involved are the periprostatic and obturator nodes. The lymphatic vessels ultimately terminate in the external and internal iliac nodal chains. Fewer than 10% of patients have involvement of presacral or presciatic nodes alone. Enlarging treatment fields to encompass lymph nodes at risk has the potential to increase treatment-associated morbidity, particularly to the small intestine and bladder. The probability of pelvic lymph node involvement depends on tumor size, stage, grade (degree of differentiation), and prostate-specific antigen serum levels. Controversy exists regarding the inclusion of pelvic nodes in large treatment portals because a survival benefit from such an approach has not been unequivocally demonstrated [22,23]. EBRT—external beam radiotherapy.





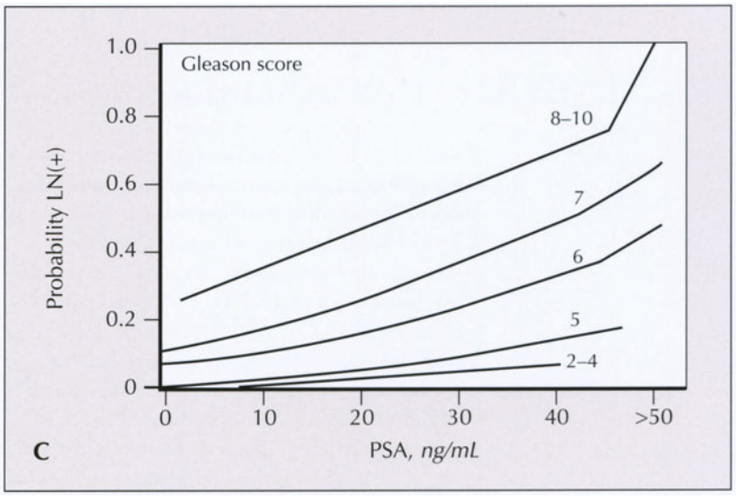
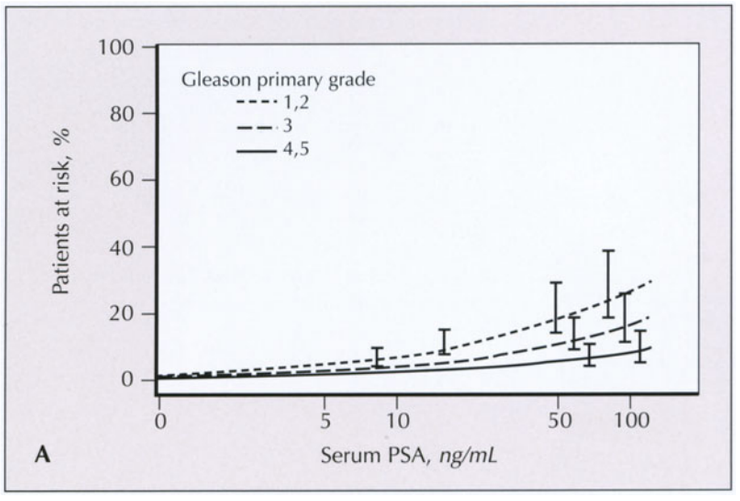


FIGURE 12-3. Probability of capsular penetration (CP+) (**A**), seminal vesicle involvement (SV+) (**B**), and lymph node involvement (LN+) (**C**) as a function of prostate-specific antigen (PSA) level and preoperative Gleason score. The extent of disease cannot be determined adequately by clinical assessment (physical examination and imaging studies), but it can be more accurately estimated using PSA level and Gleason score. This has implications with respect to correct stage assignment and, ultimately, treatment selection. Patients with a high probability of extracapsular extension or seminal vesicle involvement can be identified and offered intensive, nonsurgical therapy. (*Adapted from* Partin *et al.* [24].)



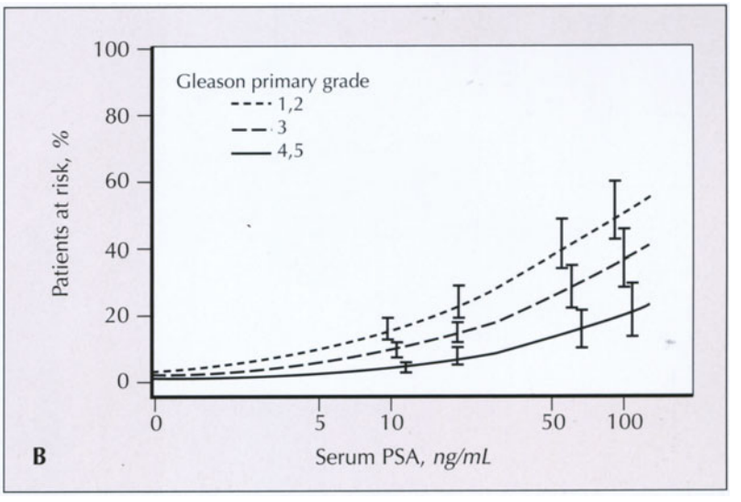


FIGURE 12-4. Risk of pelvic lymph node involvement in patients with clinical stage T1a to T2a (**A**), T2b to T2c (**B**),

(*Continued on next page*)

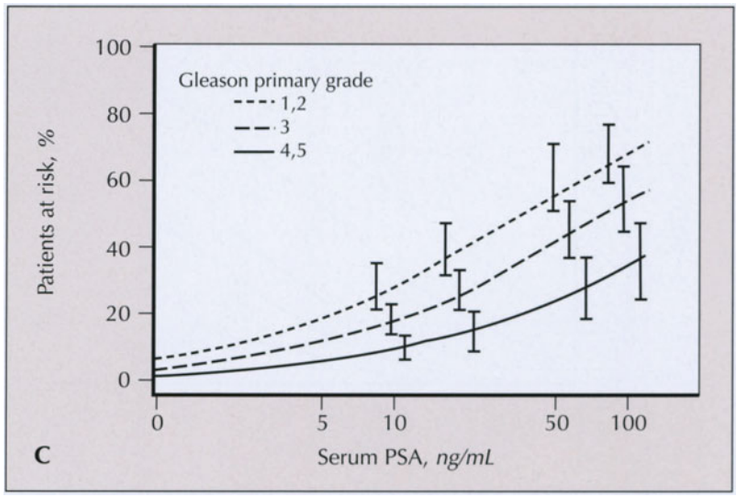


FIGURE 12-4. *(Continued)* and T3 (C) prostatic carcinoma correlated with pretherapy serum prostate-specific antigen (PSA) and Gleason primary grade.

Vertical bars represent the 95% CI for PSA values. Pelvic node status is an important predictor of prognosis and thus affects treatment selection. Pelvic lymphadenectomy studies have established that nodal metastases are a "marker" for distant disease. At 10 years of follow-up, node-positive patients have a greater than 85% chance of developing distant metastasis. That compares with a less than 20% chance in node-negative patients. The volume of nodal disease is also important, and patients with a single lymph node involved have a more favorable prognosis than those with extensive lymphadenopathy. The rate of nodal positivity is currently decreasing as a result of earlier detection through PSA testing. Node-positive patients require hormonal manipulation. The role of external beam radiotherapy in these patients is controversial and currently under study. (*Adapted from* Pisansky *et al.* [25].)

CONVENTIONAL PHOTON EXTERNAL BEAM RADIOTHERAPY

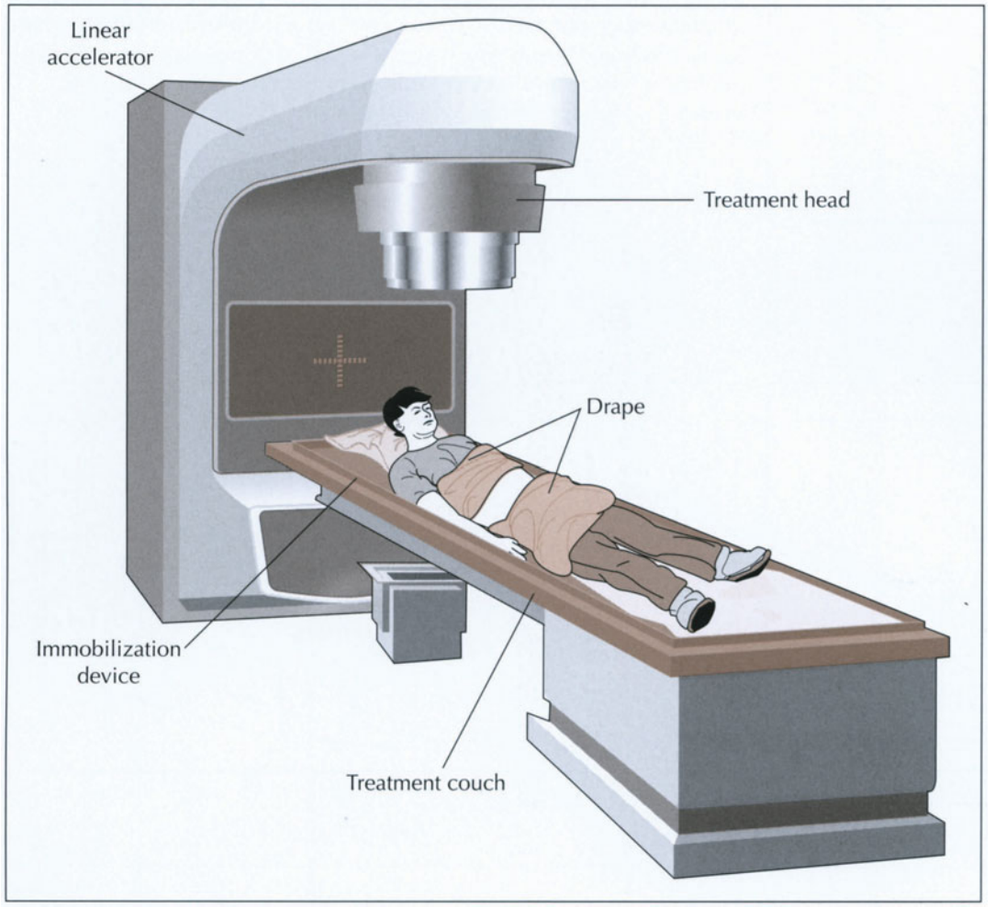


FIGURE 12-5. External beam radiotherapy (EBRT) set-up on a linear accelerator. Therapy is delivered using linear accelerators that can generate high-energy photon beams (x-rays > 10 MV). Immobilizing devices (*eg*, Alpha cradle) are used to limit day-to-day variations in position. Reference points on the patient and the immobilizer are aligned with fixed, orthogonal laser-light points that are coordinated to the treatment unit. Typically, individuals are treated in the supine position; some clinicians prefer the prone position because they believe that it may favor displacement of the prostate away from the anterior rectal wall. Prostate treatment fields are designed at the time of simulation, which precedes EBRT and constitutes the planning phase of treatment. These simulated fields are then replicated daily during treatment. Verification or "port" films are taken weekly to confirm the correct alignment of the planned fields.

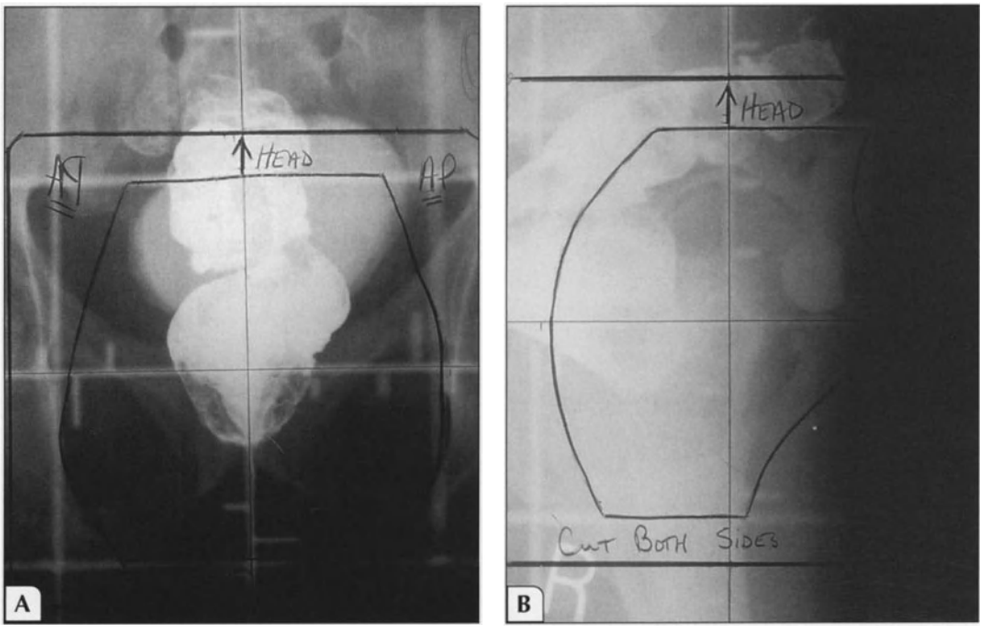


FIGURE 12-6. Conventional (non–three-dimensional) external beam radiotherapy (EBRT). This figure demonstrates radiation fields used for the treatment of prostate cancer. **A,** Anteroposterior. **B,** Right lateral. Prior to initiating EBRT, treatment planning is carried out using a simulator. This device replicates the orientation parameters and geometry of the treatment unit in every way without actually administering treatment. The typical anatomic relationship between the prostate and the pelvic bones is used to define the size and shape of the radiation fields. The bladder, urethra, and rectum may be delineated using either radiographic contrast material or the placement of a temporary urinary catheter. Typically the prostate is treated using an arrangement of two sets of opposed fields (anteroposterior and posteroanterior; right and left laterals), also called a four-field or "box" technique. Alternate field arrangements include rotational arc fields and, rarely, a three-field technique (anteroposterior; two laterals). Film records of planned treatment fields are taken and shielding blocks are drawn. These blocks (composed of lead or equivalent material) shield normal tissues from the treatment beam.

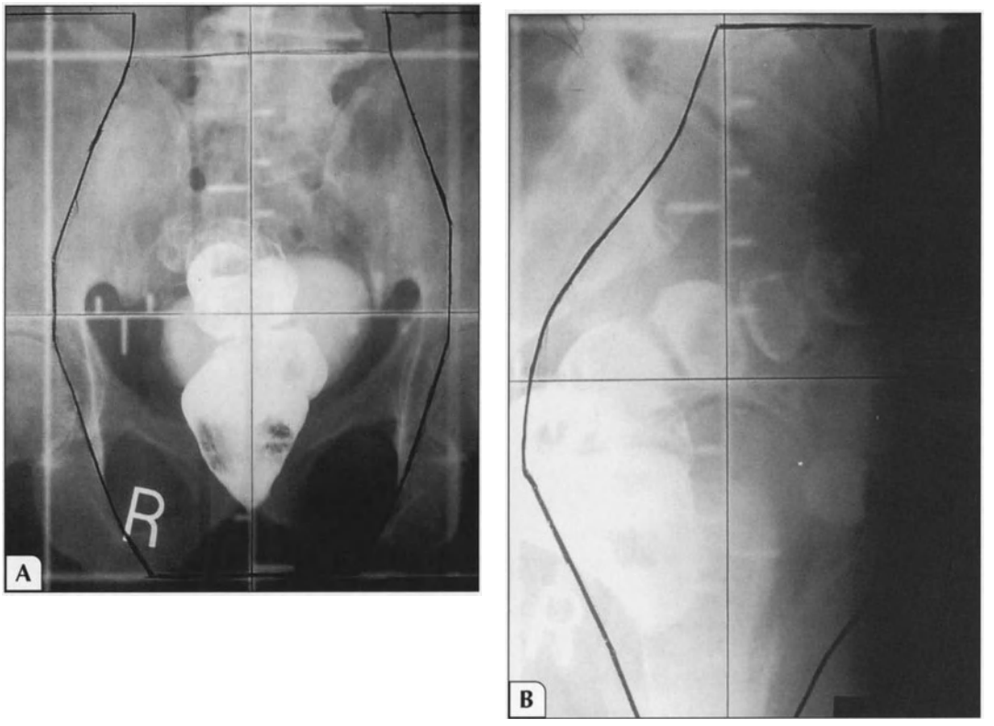


FIGURE 12-7. Conventional (non–three-dimensional) external beam radiotherapy (EBRT) fields that include the prostate and pelvic nodes. **A,** Anteroposterior. **B,** Right lateral. Controversy still exists with respect to the volumes to be used when treating prostate cancer. It has been suggested that prophylactic pelvic nodal irradiation may improve survival in patients with clinical stage T1 or T2 [22]. However, a randomized study conducted by the Radiation Therapy Oncology Group compared prostate irradiation with or without pelvic irradiation for T1b to T2 and N0M0 tumors and found no significant differences in local failure or survival [23]. Because excellent results have been achieved by use of brachytherapy or three-dimensional conformal radiotherapy targeting the prostate only, this question seems to have lost its relevance.

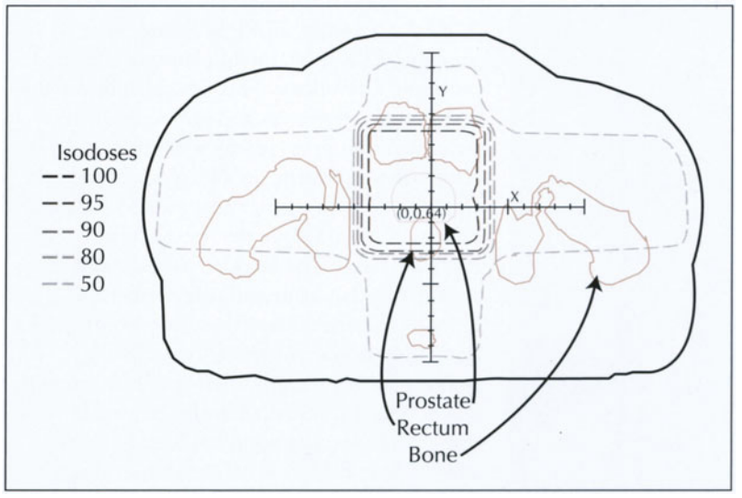


FIGURE 12-8. Axial dose distribution for a four-field "box" technique. The adequacy of delivering a prescribed dose to the volume of interest is paramount. The treatment planning software generates a series of isodose curves. These curves represent points of equal dose (usually expressed as percent-dose) and can be plotted in an axial (shown), sagittal, or coronal orientation. For any given set of isodose curves, the distribution is a function of the beam energy, the size and shape of the treatment portal, and the dimensions of the patient. Typically, the goal is to encompass the target by 100% of the prescribed dose. In conventional non–three-dimensional external beam radiotherapy a contour of the patient is taken along the central axis of the treatment field and correlated to a CT cut at approximately the same level. In this way, structures of interest such as the prostate, seminal vesicles, rectum, and bladder can be matched to the isodose plan generated.

RESULTS OF EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER

Results of Definitive Radiation Therapy for Prostate Cancer

Study	*Stage*	*Patients, n*	*Overall Survival, %*	*Disease-free Survival, %*
Bagshaw *et al.* [26]	T1*	335	60	60
Hanks [27]	T1b	116	63	52
Perez *et al.* [28]	T1b	48	70	60
Bagshaw *et al.* [26]	T2*	242	53	39
Hanks [27]	T2	415	46	34
Perez *et al.* [28]	T2	252	65	56
Bagshaw *et al.* [26]	T3	385	38	50
Hanks [27]	T3	296	32	26
Perez *et al.* [28]	T3	412	42	38

**Stanford staging system.*

FIGURE 12-9. Results of definitive radiation therapy for prostate cancer (selected studies with 10-year follow-up). Because of the long natural history of prostate cancer, the impact of cancer-related death on survival can be appreciated only with long follow-up. Recently, biochemical freedom-from-relapse and biochemical disease-free survival have been introduced as surrogate endpoints. Despite heavy reliance of modern clinical research on these endpoints, their validity has not yet been established. The data presented here originate in the pre–prostate-specific antigen era. Nonetheless, in comparing such results with the surgical literature, the American Urological Association concluded that external beam radiotherapy (EBRT) and radical prostatectomy offer equivalent treatment benefits to patients with early stage disease [29]. For locally advanced disease, the studies demonstrate that conventional EBRT alone can result in long-term survival of only a minority of patients, thus necessitating alternative approaches to the management of this stage.

Moderate and Severe Late Complications of Conventional (Nonconformal) EBRT for Prostate Cancer

		Genitourinary, %			Gastrointestinal, %				
Series	Patients, n	Hematuria/Cystitis	Stricture	Incontinence	Rectal	Small Intestine	Fistula, %	Other	Death, %
Stanford [30]	802	9.5*	9.5*	9.5*	4.4†	4.4†	0	1.7‡	0
RTOG [31]	453	4.4	5.1	0	3.3	0.4	0	0	0
Mallinckrodt [32]	577	2.9	4.5	0.1	5.9	2.0	0.5	3.6§	0.1
Johns Hopkins [33]	240	4.6	6.6	3.0	10.8	1.0	0	3.5‡	0

*Includes all genitourinary complications.
†Includes all gastrointestinal complications.
‡Genital and leg edema.
§Pubic bone necrosis, genital and leg edema, subcutaneous fibrosis, and skin necrosis.

FIGURE 12-10. Sequelae of conventional non–three-dimensional planned external beam radiotherapy (EBRT). Conventional EBRT is generally well tolerated. The majority of patients will experience acute mild to moderate gastrointestinal and genitourinary symptoms. Side effects tend to develop in the latter part of a treatment course and usually resolve within weeks of ending irradiation. Persistent symptoms and late (> 3 months) complications are infrequent and likely associated with more profound parenchymal injury. The risk of late complications in conventional EBRT is associated with higher radiation doses (> 70 Gy), higher volume of normal tissues in the treatment field (*eg*, anterior rectal wall), and patient comorbidities. Sexual function after prostate irradiation has not been well studied; the literature suggests reduced potency in up to 60% of men, but most such studies do not account for the pretherapy erectile function and comorbid conditions of the patients. RTOG—Radiation Therapy Oncology Group.

ADVANCES IN TREATMENT OF PROSTATE CANCER USING EXTERNAL BEAM RADIOTHERAPY

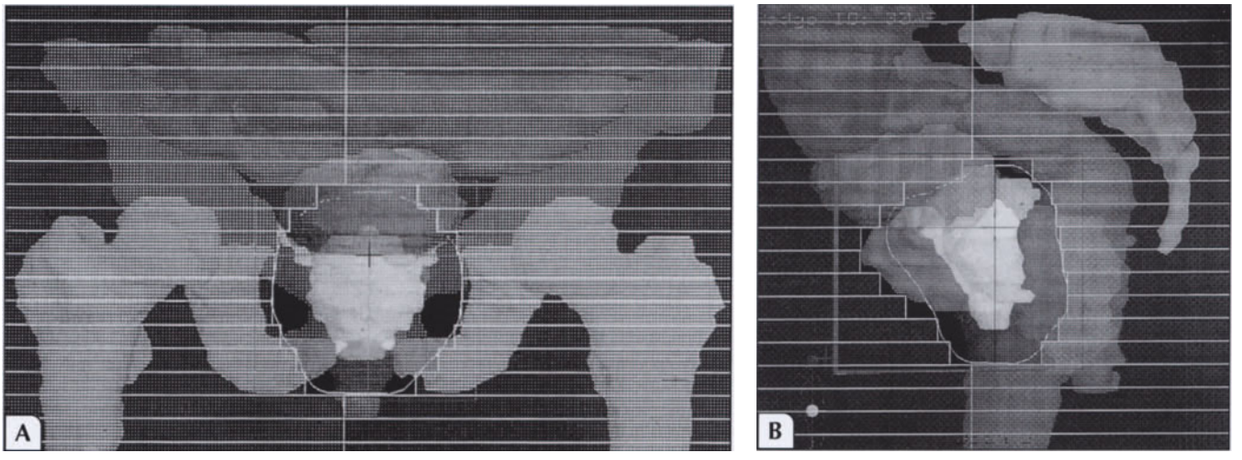
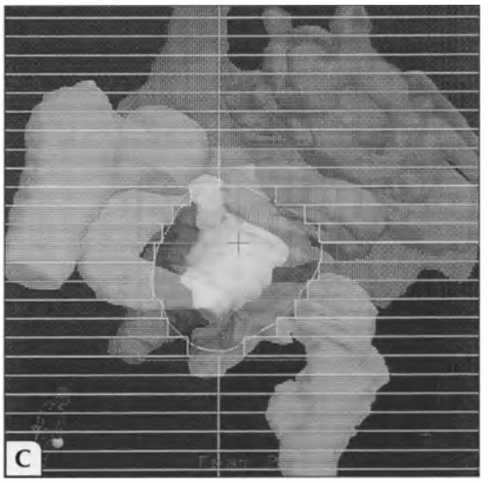


FIGURE 12-11. Three-dimensional (3D) treatment planning of external beam radiotherapy for prostate cancer. Current studies have shown that CT-based 3D treatment planning can reduce the acute and late toxicity of radiotherapy [34,35]. These figures show a beam's-eye-view reconstruction of the prostate, seminal vesicles, bladder, rectum, pelvic bones, and small intestine in an anteroposterior (**A**), lateral (**B**),

(*Continued on next page*)



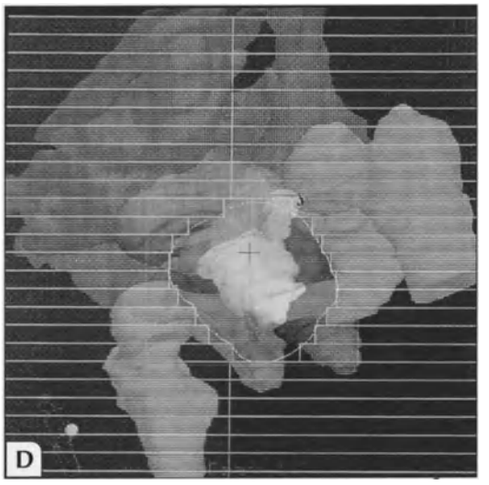
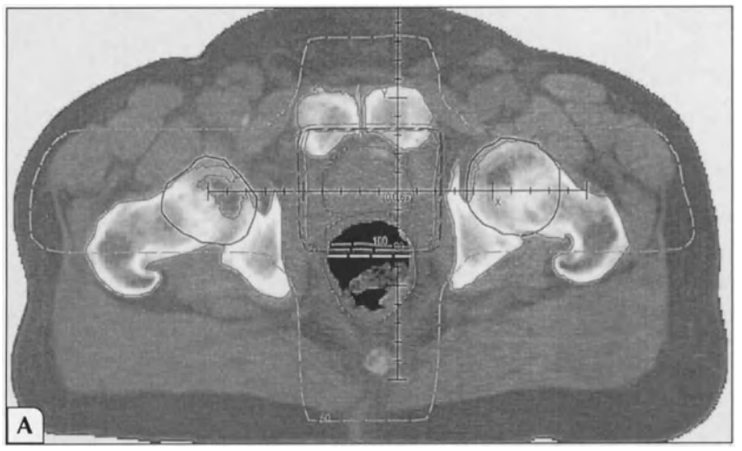


FIGURE 12-11. *(Continued)* right anterior inferosuperior oblique (**C**), and left anterior inferosuperior oblique (**D**) projections. The *solid white line* represents the edge of the fields that were designed to encompass the prostate gland with margins. To generate these projections, the patient is scanned in the treatment position in an immobilization device (used throughout the treatment course to minimize movement and daily set-up errors), with radiopaque markers placed over localization points. The gross tumor volume (GTV) includes the tumor as visualized. The clinical target volume (CTV) includes the GTV plus the regions considered at risk for microscopic tumor spread. The planning target volume (PTV) includes the CTV plus an additional margin to allow for patient set-up errors and organ motion. The GTV and surrounding organs of interest are identified and their contours are entered on each CT slice on which they appear, using a tracking device. The isocenter is identified and the 3D coordinates of its position are also entered. The PTV and the other organs of interest are reconstructed graphically in three dimensions. Their projection is displayed as seen from the beam's source (beam's-eye view), which enables the radiation oncologist to design beams that conform to the shape of the target.



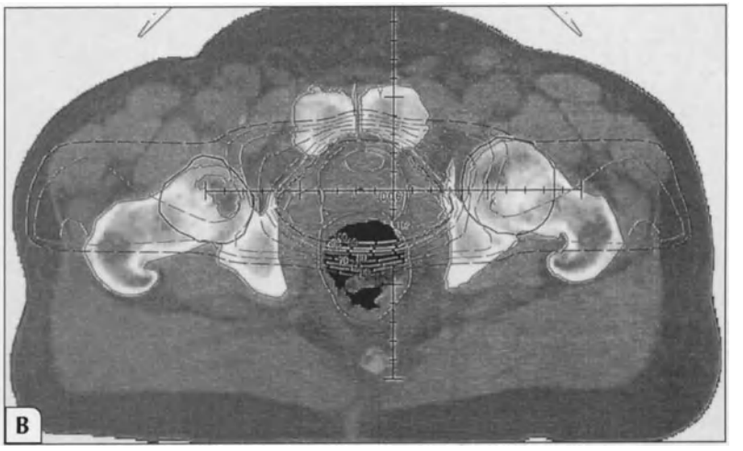
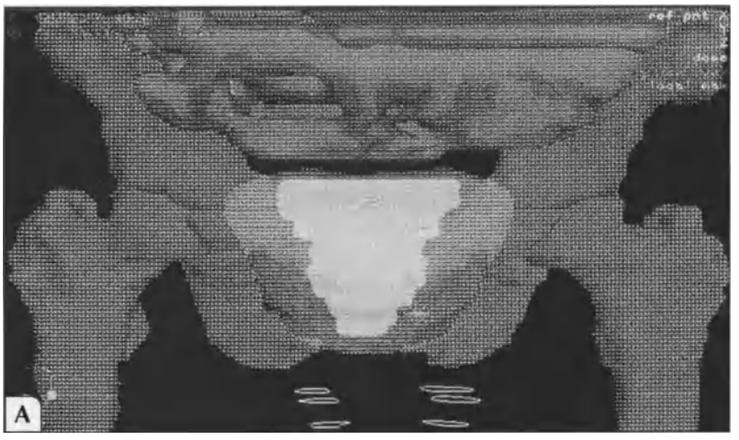


FIGURE 12-12. Two-dimensional dose distribution and evaluation of plans. The dose distribution is computed for each field separately. Most plans involve the use of multiple fields of radiation. Once these fields are specified and weighted (each field is assigned its relative contribution to the total dose), dose computation can be carried out. This figure depicts dose distribution of a four-field "box" technique (**A**) and a nonaxial technique (**B**) at the level of the central axis. The distribution of dose can be readily related to the relevant anatomy.



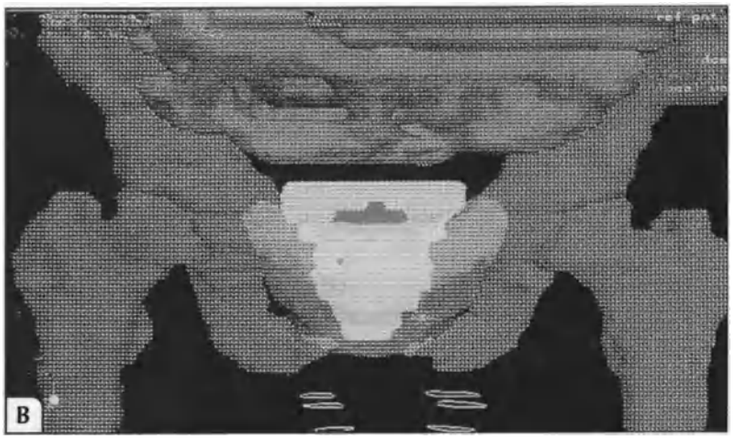


FIGURE 12-13. Three-dimensional (3D) dose distribution and evaluation of plans. A unique feature of 3D treatment planning systems is the ability to display the distribution of dose superimposed on any reconstructed axial, sagittal, coronal, or oblique plane. In addition, the distribution of dose can be viewed in three dimensions as isodose envelopes covering 3D reconstructions of the target and adjacent organs. This figure depicts the distribution of dose viewed from an anteroposterior perspective. Note that while the 98% isodose envelope covers the target completely (**A**), the 100% isodose envelope leaves a region in the superior aspect of the gland uncovered (**B**). This tool allows easy identification of target regions that are under- or overdosed.

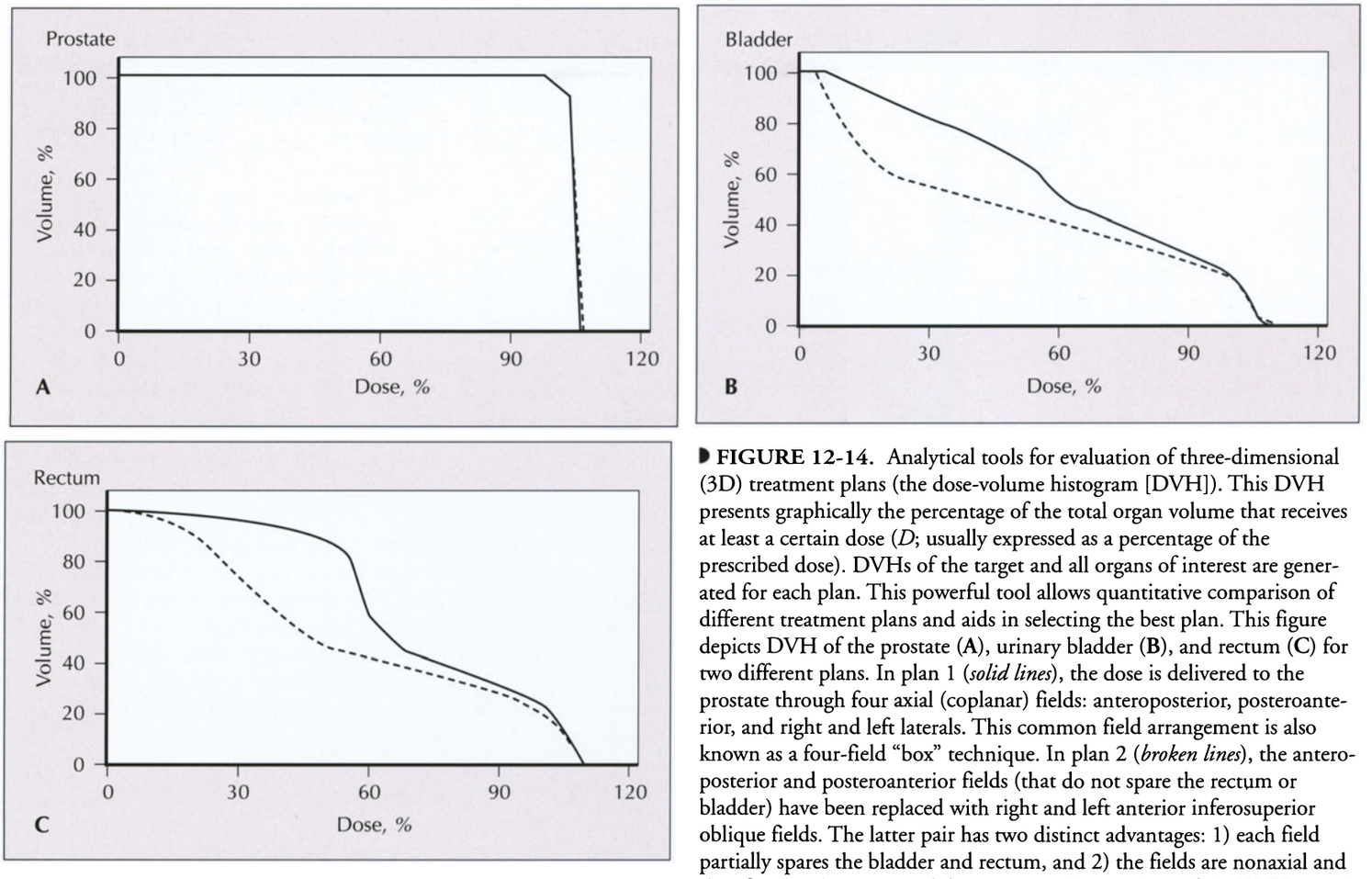


FIGURE 12-14. Analytical tools for evaluation of three-dimensional (3D) treatment plans (the dose-volume histogram [DVH]). This DVH presents graphically the percentage of the total organ volume that receives at least a certain dose (*D*; usually expressed as a percentage of the prescribed dose). DVHs of the target and all organs of interest are generated for each plan. This powerful tool allows quantitative comparison of different treatment plans and aids in selecting the best plan. This figure depicts DVH of the prostate (**A**), urinary bladder (**B**), and rectum (**C**) for two different plans. In plan 1 (*solid lines*), the dose is delivered to the prostate through four axial (coplanar) fields: anteroposterior, posteroanterior, and right and left laterals. This common field arrangement is also known as a four-field "box" technique. In plan 2 (*broken lines*), the anteroposterior and posteroanterior fields (that do not spare the rectum or bladder) have been replaced with right and left anterior inferosuperior oblique fields. The latter pair has two distinct advantages: 1) each field partially spares the bladder and rectum, and 2) the fields are nonaxial and therefore overlap to a much lesser extent. Comparison of the DVHs reveals that whereas the coverage of the prostate remains unchanged, the volumes of bladder and rectum that receive the higher doses are reduced in plan 2.

Studies on Androgen Deprivation and Radiotherapy

Study	Patients, n	8-Year Biochemical DFS, %		8-Year Survival, %	
		Control Arm	Study Arm	Control Arm	Study Arm
RTOG 86-10 [6]	471	3	16*	44	53
RTOG 85-31 [7]	945	8	32*	47	49
MDA [8]	78	51†	66*†	73	68
EORTC [9]	415	44	85*	58	78*

*Statistically significant differences between the study and control arms.
†Clinical disease-free survival; PSA data not available for analysis.

FIGURE 12-15. Androgen deprivation and radiotherapy. Androgen deprivation has been combined with radiotherapy in an attempt to enhance prostate cancer cell kill. The table summarizes the results of four major prospective randomized clinical trials of this combination therapy. The Radiation Therapy Oncology Group (RTOG) trial 86-10 randomly assigned 471 patients to radiotherapy alone or 4 months of androgen deprivation before and during radiotherapy. With a median follow-up time of 8.6 years, the 8-year local control and biochemical disease-free survival were 42% versus 30% and 16% versus 3%, respectively [6]. RTOG trial 85-31 [7] randomly assigned 945 patients to immediate therapy with luteinizing hormone-releasing hormone agonist or the same androgen suppression at time of relapse. Although local control and disease-free survival (DFS) were improved, there was no statistically significant impact on overall survival. Subset analysis of centrally reviewed Gleason 8–10 patients who did not undergo prostatectomy showed a significant overall and cause-specific survival advantage. At the MD Anderson (MDA) Cancer Center, Dallas, 78 patients with stage C prostate cancer were randomly assigned to receive radiotherapy with or without adjuvant estrogen. DFS in the adjuvant group was significantly higher than in the radiation-only group. At 5, 10, and 15 years, DFSs were 66%, 58%, 58%, and 51%, 46%, 37% in the adjuvant and control groups, respectively [8]. The benefit of early hormonal intervention was attributed to suppression of the emergence of distant metastases. Early estrogen administration was also associated with a trend toward higher local control, but the difference did not reach significance. The European Organization for Research and Treatment of Cancer (EORTC) conducted a multicenter prospectively randomized trial in patients with high-grade T1 to 2 or T3 to 4 prostate cancer. A total of 415 patients were randomly assigned to radiotherapy with or without 3 years of hormonal therapy. With a median follow-up time of 36 months, they reported a significant improvement in local control, DFS, and, most importantly, a survival advantage (78% vs 56%) for those patients treated with hormones [9]. PSA—prostate-specific antigen.

A. High-dose Radiotherapy: Toxicity Data

Institution	Patients, n	Dose level, Gy	Median Follow-up, mo	Severe Complications
MSKCC [37]	59	75.6	14	0
	21	81		0
FCCC [38]	136	71–73.99	36	1.8†
	130	74–76.99		4.5†
	19	77–79.99		12.3†
WSU [39]	25	78‡	20	0
	24	82.8§		0

*Grades 3 and 4.
†Gastrointestinal complications.
‡1.3 Gy twice daily.
§1.15 Gy twice daily.

FIGURE 12-16. High-dose radiotherapy: toxicity and efficacy data. **A,** In recent years, along with the increased use of prostate-specific antigen (PSA) in follow-up, it has become clear that standard treatment options for patients with locally advanced prostate cancer are suboptimal. Investigational efforts have focused on increasing the tumoricidal impact of therapy by increasing the physical dose, the biologic effective dose, or by combining radiotherapy with other tumoricidal treatments. The Patterns of Care study provided some evidence for a dose-response in prostate cancer [36]. Total doses in excess of 70 Gy were associated with an increase in local control. Unfortunately, such doses were also associated with an unacceptable complication rate. A number of phase I dose-escalation studies have been completed and have demonstrated that higher doses can be delivered safely using three-dimensional treatment planning. This figure summarizes the results of these studies at Memorial Sloan-Kettering Cancer Center (MSKCC), New York; Fox Chase Cancer Center (FCCC), Philadelphia; and Wayne State University (WSU), Detroit. With the exception of the results from FCCC, severe late complications appear to be lower than what has been reported with traditional treatment planning and conventional doses.

(*Continued on next page*)

B. High-dose Radiotherapy: Efficacy Data

Study	Patients, n	Risk Group	Dose Level, Gy	DFS, %
Zelefsky *et al.* [1]	743	Intermediate	75.6–81.0	79*
			64.8–70.2	53*
		High	75.6–81.0	59*
			64.8–70.2	33*
Hanks *et al.* [2]	714	All	≥ 74	71†
			< 74	56†
Pollack *et al.* [3]	1127	Intermediate/high	> 77	68*
			67–77	51*
Kupelian *et al.* [4]	1041	All	≥ 72	87†
			< 72	51†

*Four-year rate.
†Eight-year rate.

FIGURE 12-16. *(Continued)* **B,** The results from a number of retrospective series of high-dose radiotherapy are shown. Statistically significant improvements in local control and disease-free survival have been uniformly demonstrated. Pollack *et al.* [5] reported recently on a randomized radiotherapy dose-escalation study comparing 70 with 78 Gy for prostate cancer. A total of 305 stage T1–3 patients were randomly assigned. With a median follow-up of 40 months, there was a marginally significant (P = 0.058) difference in 5-year freedom from biochemical or disease failure (69% and 79% for the 70- and 78-Gy groups, respectively). Multivariate analysis showed that the dose level was an independent correlate of outcome, along with pretreatment PSA, Gleason score, and stage. A comprehensive review of dose-response in prostate cancer [40] examined the relationship between dose and local control, biochemical control, and survival. A total of 11,297 patients in 22 reports were reviewed. Of the 11 series addressing the association of dose with local control, nine showed statistically significant improvements. All 12 series that reported biochemical control showed statistically significant improvements, and three of nine series showed statistically significant improvements in survival. Today, the impact of total radiation dose on survival remains unclear. Other important questions that remain unresolved include the benefit of high-dose therapy in low-risk prostate cancer patients, and whether the benefit of androgen deprivation and high-dose therapy are additive. DFS—disease-free survival.

Neutron Radiotherapy for Locally Advanced Prostate Cancer

Study	Patients, n	Dose to Prostate	5-Year Local Control %	5-Year Biochemical DFS, %	5-Year Survival, %
NTCWG 8523 [41]					
Control arm	85	70–70.2 Gy	78*	55*	73
Study arm	87	20.4 NGy	89	83	68
RTOG 7704 [42]					
Control arm	36	70 Gy†	61*	NA	13*
Study arm	55	70 Gy†	81	NA	63

*Statistically significant differences between the study and control arms.
†Photon equivalent dose. Patients were treated with a mixture of 40% neutrons and 60% photons. The daily neutron dose was adjusted at each institution, depending on the relative biologic effectiveness of the beam, so that equivalent biologic doses of neutrons or photons were given each day.

FIGURE 12-17. Neutron radiotherapy for locally advanced prostate cancer. Fast neutrons are heavy subatomic particles with distinct radiobiologic advantages over photons. Cell kill with neutrons is less sensitive to the effects of tumor hypoxia (a major contributing factor to radioresistance), cell-cycle kinetics (cells in G0 are relatively resistant to photons), and repair of sublethal damage. The Radiation Therapy Oncology Group (RTOG) conducted a prospective randomized trial (RTOG 77-04) comparing a mixture of photons and neutron beams with photon radiotherapy in patients with locally advanced prostate cancer. At 8 years, the actuarial survival was 63% and 13% in the mixed beam and photon cohorts, respectively (P = 0.001). After correction for non–cancer-related deaths, there was still a significant advantage to the neutron-photon arm (82% vs 54%, P = 0.02). There was also a significant difference in local control (77% vs 31%, P = 0.01). In another trial, conducted by the Neutron Therapy Collaborative Working Group (NTCWG 8523), patients were randomly assigned to neutron or photon therapy. With a median follow-up of 68 months, there were significant differences in local control (87% vs 68%, P = 0.01) and disease-free survival (83% vs 55%, P < 0.001), but not in survival [19]. A significant increase in severe morbidity was noted in the neutron arm; grade 4 complication occurred in 10 of 87 patients in the neutron group (including six colostomies), but in only one of 85 in the photon arm. Complications were mostly confined to institutions where neutron beam shaping was not available. With modern equipment and with the aid of three-dimensional treatment planning, neutron radiotherapy can be delivered without excessive complications [43]. DFS—disease-free survival; NA—not available.

A. Adjuvant Radiotherapy Results: Summary of Recent Studies with No Biochemical or Only Partial Biochemical Relapse Data

Study	Patients, n	Median Dose, Gy	DFS, %
Petrovich *et al.* [10]	311	48	51 (10-y)
Syndikus *et al.* [11]	89	50–55 (range)	75 (7-y)
Anscher *et al.* [12]	46	55–65 (range)	55 (10-y)

B. Adjuvant Radiotherapy Results: Summary of Recent Studies on Patients with Positive Resection Margins or pT3 Disease

Study	Patients, n	Median Dose, Gy	DFS, %
Schild *et al.* [13]	60	62	57 (5-y)
Catton *et al.* [14]	54	60	80 (5-y)
Vicini *et al.* [15]	38	59.4	67 (5-y)
Morris *et al.* [16]	40	60–64 (range)	81 (3-y)
Valicenti *et al.* [17]	52	64.8	90 (3-y)

FIGURE 12-18. Adjuvant radiotherapy results. **A**, Approximately one third of patients suffer a biochemical relapse within 5 years of radical prostatectomy. A number of adverse clinical and pathologic features, such as a high initial prostate-specific antigen (PSA) level, high Gleason score, involved surgical margins, and involved seminal vesicles predict for a higher failure rate. Postoperative radiotherapy has been used in such patients as an adjunct or as salvage therapy for those with biochemical or clinical evidence of residual or recurrent disease. This table provides a summary of the largest adjuvant radiotherapy series with no biochemical or only partial biochemical relapse data. All authors found an advantage for adjuvant radiotherapy when compared with observation. Petrovich *et al.* [10] compared the outcome in 311 patients with pT3N0 adenocarcinoma of the prostate treated with surgery and radiotherapy with that in 91 patients with more favorable disease treated with surgery alone. Radiotherapy reduced the incidence of local recurrence in the high-risk group to that of the low-risk group. Syndikus et al. [11] found that the local recurrence rates were significantly decreased in the early postoperative radiotherapy group compared with the surgery only group. In a multivariate analysis, the lack of postoperative radiotherapy was identified as a significant adverse factor. Anscher *et al.* [12], similarly, reported a significant improvement of local control with adjuvant radiotherapy (10-year rates of 92% vs 60%, $P = 0.002$). These retrospective reviews document a consistent improvement in local control, but no apparent effect on the risk of subsequent systemic relapse or survival.

B, Adjuvant radiotherapy for patients with positive resection margins or pT3 disease. Only series with full biochemical relapse data are included. Although this approach is associated with excellent outcome, it represents excess therapy for a substantial number of patients who are destined to do well with surgery alone. The Southwest Oncology Group (SWOG) has completed a phase III randomized trial of immediate versus delayed postoperative radiotherapy for such patients. The results of this study will not be available for a few more years. An ongoing European Organization for Research and Treatment of Cancer (EORTC) trial addresses the same question. Controversies continue to exist in regard to selection criteria for therapy, the need for androgen deprivation in this setting, optimal radiation dose, and treatment techniques. Although some authors report that focally positive margins do not carry excess risk of failure [44], others have shown a significant advantage of adjuvant radiotherapy for patients with pT2N0 disease and a single positive margin [45]. A secondary analysis of RTOG 85-31 [46] showed a statistically significant advantage to postoperative radiotherapy combined with androgen deprivation compared with radiotherapy alone (5-year disease-free survival [DFS] of 65% vs 42%, $P = 0.002$). RTOG trial 96-01 is now comparing radiotherapy plus placebo to radiotherapy plus bicalutamide in this setting.

Results of Salvage Radiotherapy for Prostate-specific Antigen Failure After Radical Prostatectomy

Study	Patients, n	Median Pre-RT PSA	Median Dose, Gy	DFS, %
Pisansky *et al.* [18]	166	0.9	64	46 (5-y)
Anscher *et al.* [19]	89	1.4	66	50 (4-y)
Cadeddu *et al.* [20]	82	2.8	64	10 (5-y)
Nudell *et al.* [21]	69	0.1–29.3 (range)	60–74 (range)	47 (4-y)
Catton *et al.* [14]	43	0.2–24.8 (range)	60	20 (5-y)

FIGURE 12-19. Results of salvage radiotherapy (RT) for prostate-specific antigen (PSA) failure after radical prostatectomy. This table provides results of the largest series reported with a median follow-up of at least 3 years. Pisansky *et al.* [18] described the outcome of 166 men receiving salvage RT at the Mayo Clinic between 1987 and 1996, for a detectable PSA of 0.2 ng/mL or greater following radical prostatectomy. Biochemical failure was defined as either the commencement of androgen deprivation, a post-RT PSA greater than the pre-RT value, or two PSA values both greater than 0.3 ng/mL and greater than the post-RT nadir. With a median follow-up of 52 months, the actuarial 5-year freedom from biochemical failure was 46% (95% CI, 38%–55%), and on multivariate analysis, the significant factors associated with an increased risk of failure were higher pre-RT PSA, Mayo tumor grade 3 or 4, and pathologic seminal vesicle involvement.

Anscher *et al.* [19] reported on 89 men treated with salvage RT between 1987 and 1997. Biochemical failure was defined as the start of androgen-deprivation therapy, or an increase in PSA of 10% on two consecutive determinations at least 1 month apart. With a median follow-up of 48 months, the actuarial 4-year biochemical disease-free survival (DFS) was 50. On univariate analysis, dose greater than 65 Gy, use of conformal technique, preradiation PSA of less than 2.5 ng/mL, undetectable PSA after radical prostatectomy, and greater than 180 days from radical prostatectomy to biochemical failure were significant favorable prognostic factors. On multivariate analysis, only radiation dose greater than 65 Gy remained significant. Most series report an association between the level of serum PSA just prior to RT and ultimate outcome. However, a variety of cut-off PSA values have been used in these analyses (typically between 1 and 2 ng/mL), none more useful than another. Today, there is no PSA value above which RT has been shown to be totally ineffective.

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Permanent Seed Interstitial Prostate Brachytherapy

13

Mark A. Ritter

Permanent implant prostate brachytherapy first gained popularity in the 1970s but subsequently underwent more than a 10-year period of near abandonment. Loss of interest in the technique stemmed from technical limitations of the retropubic approach that often resulted in poor physical distribution of the implanted seeds. This, together with inappropriately chosen patients, often led to poor long-term results and a loss of enthusiasm for the technique. Improving external beam and surgical techniques also contributed to this shift in emphasis.

Development of techniques for transrectal ultrasound of the prostate has provided sufficient intratreatment imaging guidance needed to produce better seed distributions. This, together with maturing follow-up data that indicate biochemical control rates similar to those achieved with radical prostatectomy and modern external beam radiotherapy, has led to an initially gradual but now rapidly accelerating reemergence of the approach.

Inclusion of multiple professional disciplines is necessary for successful implementation of an implantation program. The medical judgment of the participating urologist and radiation oncologist is key in selecting the most appropriate patients for the procedure. The nursing element is essential in advising the patient about and coordinating the logistics of the procedure. A sound, well-organized physics-related and dosimetric effort is essential both in the preimplantation phase of the process, as well as in the postimplantation quality control that provides feedback to the clinicians regarding the technical quality of the brachytherapy process.

This review focuses on the most prominent technical approach, which is that of ultrasound-based planning and permanent seed implantation. Whether carried out in two temporally discrete steps or performed during the same intraoperative session, the essential elements are the same. Another less common but emerging variation is that of temporary, high dose–rate (HDR) brachytherapy. This approach is only discussed in broad terms here and the interested reader is directed to the appropriate sources that describe this technique in greater detail. Several training courses are available in the United States that offer instruction in permanent and HDR temporary prostate brachytherapy. Enrollment in these courses is essential for practitioners who are establishing a prostate brachytherapy program.

Relative Contraindications

Severe voiding symptomatology
Large prostate
Major pubic arch shadowing of the prostate
Prior transurethral resection of the prostate
Patients with unfavorable clinical, biochemical, and pathologic characteristics

FIGURE 13-1. The ideal candidate for prostate brachytherapy shares some of the same characteristics as the patient considered eligible for radical prostatectomy. Such patients should have clinically localized prostate cancer and a reasonable life expectancy—perhaps 10 years or longer. A lack of agreement exists about contraindications for the procedure. Other than rather clear-cut situations such as metastatic disease, several clinical circumstances that have been accepted by some clinicians but not others as contraindications. These findings include severe voiding symptomatology, a large prostate, pubic arch shadowing of the prostate when viewed from a transperineal approach (*ie*, pubic arch interference), previous transurethral resection of the prostate, and patients with unfavorable clinical, biochemical, and pathologic characteristics.

Urinary symptomatology: Several reports have indicated correlations between high pretreatment American Urological Association scores or large postvoid residuals and subsequent postimplantation urinary retention [1,2]. However, although the correlations seem real, significant data scatter makes either of these factors poor predictors in individual cases of the likelihood of significant toxicity. However, a high level of urinary symptomatology remains at least a relative contraindication for prostate brachytherapy.

Large prostate: In addition to the correlation between large prostate volume and pubic arch interference (discussed later in this chapter), some other data also suggest that a large size [2] or substantial median lobe hyperplasia [3] correlate with subsequent urinary difficulties. Again, however, at this point, data are insufficient to reach a conclusion that these factors are reliable predictors of postimplant retention.

Prior transurethral resection: An early report [4] indicated a higher risk of urinary incontinence in patients who had previously undergone at TURP. However, this was also from an institution that previously performed uniform seed loading rather than the modified peripheral load that they later adapted and most institutions now use (see later discussion). A modified peripheral leading can substantially reduce urethral doses and it now appears that TURP can in fact be implanted without undue risk of urinary incontinence [5].

Patients with Unfavorable Clinical, Biochemical, and Pathologic Characteristics

Category	*PSA and Gleason Score Ranges*
Favorable	PSA < 10 ng/mL; Gleason score < 7
Intermediate	PSA > 10 *or* Gleason score < 7
Unfavorable	PSA ≥ 10 *and* Gleason score 7

FIGURE 13-2. Unfavorable clinical, biochemical, and pathologic characteristics. Patients can be grouped according to prostate-specific antigen (PSA) and Gleason score ranges that define their prognosis fairly independently of whether they choose a surgical or a radiation therapy treatment approach. The presence of perineural invasion in the biopsy should also be considered as unfavorable. Although unfavorable characteristics also increase the risk of distant disease and require that an adequate metastatic work-up (bone scan, CT scan) be performed, they also increase the risk of extraprostatic extension of disease [6]. Concern has been expressed that prostate brachytherapy alone might not provide sufficient dosimetric coverage beyond the prostate borders to adequately treat such more likely extraprostatic extensions in the higher risk patient. Alternate proposed approaches often include external beam radiotherapy along or a combination of external beam therapy with an implant. However, data currently available with long-term follow-up fails to demonstrate that a combined external beam–implant approach is far superior to an implant alone in these patients with less favorable characteristics [7].

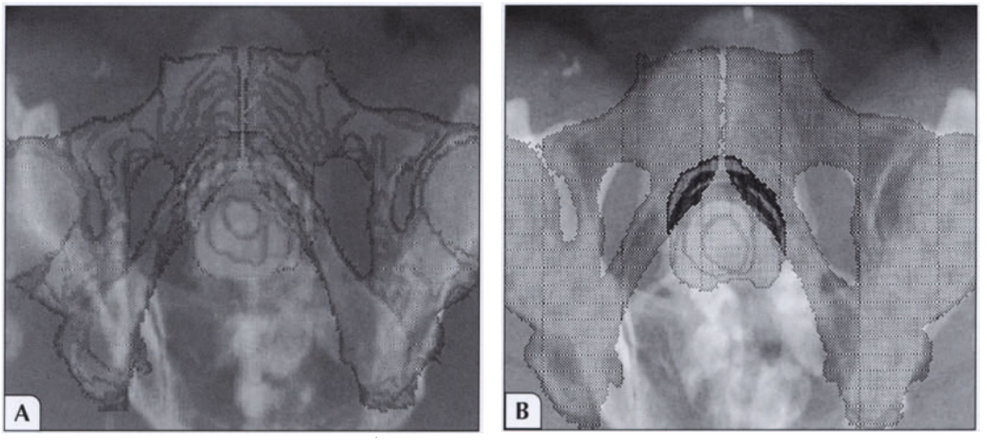

FIGURE 13-3. Pubic arch shadowing of the prostate can sometimes create difficulties in implanting the anteriolateral regions of the prostate. This is a problem that certainly correlates with prostate size but that also depends on the breadth of the pelvis. It is possible to have a quite large prostate in a wide pelvis that can be implanted without difficulty yet have a smaller prostate in a narrow pelvis that creates significant technical difficulty. Some investigators have carried out CT-based evaluations of pubic arch interference, but it is also possible to define the likely degree of interference directly from the preimplant ultrasound based planning study in which the frame containing the narrowest section of the pubic arch can be superimposed on the frame containing the widest section of the prostate.

Even significant interference can sometimes be overcome, particularly when it can be recognized at the time of the planning ultrasound study. Reangulation of the ultrasound probe to an angle parallel to the table can sometimes significantly reduce the degree of interference. Alternatively, needles can often be reangled during the implant process to avoid bone, sometimes in freehand fashion. Overall, however, one should be cognizant of the potential for pubic arch interference. Where such interference is substantial, many clinicians pretreat the patient with several months of luteinizing hormone–releasing hormone (LHRH) agonist therapy, which can result in a prostate volume reduction of between 5% and 50%, as seen in these CT-reconstructed transperineal views of the prostate before (**A**) and after (**B**) a 3-month treatment with an LHRH agonist.

PREOPERATIVE EVALUATION

Preoperative Evaluation

Prostate-specific antigen
Grade
Clinical stage
Percentage replacement and location of biopsy cores
Urinary symptom scores
Prostate size
CT and bone scan optional

FIGURE 13-4. Preoperative, oncologic evaluation for a patient considering prostate brachytherapy. This evaluation is essentially no different from that for a patient considering radical prostatectomy or localized external beam radiotherapy. Clinical parameters including prostate-specific antigen (PSA), grade, clinical stage, and the percentage of replacement and location of the positive biopsy cores. Bone scans and CT scans of the abdomen and pelvis are usually not performed, given the generally low frequency with which these tests produce positive results in this group of patients. Urinary symptom scores are obtained. If a significant level of obstructive symptoms is determined, a trial of α-blockade is often carried out. Very large prostates may require reduction using hormonal therapy, as discussed previously.

TREATMENT SELECTION

Selection of Therapy

Isotope selection
Brachytherapy alone or with external beam radiotherapy
Hormonal therapy

FIGURE 13-5. Selection of therapy.

Isotope selection: The two most commonly used radioisotopes for prostate brachytherapy are ^{125}I and ^{103}Pd. Each has certain potential physical and theoretical advantages. ^{125}I, with more energetic x-rays than ^{103}Pd, may depend less on attaining an optimal seed distribution to achieve adequate dosimetric coverage of the entire prostate, whereas ^{103}Pd, with its shorter half-life of decay (17 days for $^{1\text{-}3}$Pd vs 60 days for ^{125}I) and resulting high rate of dose delivery, may be more suitable for higher grade tumors with higher cellular proliferation rates [8]. Newer data also suggest that prostate cancers have a higher intrinsic ability to repair sublethal radiation damage [9] and, if true, this would favor the ^{103}Pd isotope because its higher dose rate should allow less time for repair to occur. The fact is, however, that there had never been any clear-cut data to support an advantage of the use of one isotope over another [10]. This suggests that currently recommended dose prescriptions for each isotope have roughly equivalent biologic effectiveness.

Brachytherapy with or without external beam radiotherapy: Several clinical groups add an external beam radiotherapy component to prostate brachytherapy, either before or after the brachytherapy. Other groups use the external beam component only for higher risk patients (higher grade, tumor stage, or prostate-specific antigen [PSA]) with a greater risk for extracapsular disease. Potential advantages of the combined approach include a wider treatment margin and the ability to smooth out somewhat any dosimetric heterogeneities in the implant itself. However, despite these potential advantages, there is a lack of conclusive evidence that combined therapy is better than brachytherapy alone [7]. The issues of added cost, inconvenience, and potential toxicities to the patient must also be considered.

Hormonal therapy: As discussed previously, luteinizing hormone–releasing hormone (LHRH) agonist pretreatment has primarily been used to reduce the volumes of unmanageably large prostates to volumes where pubic arch obstruction is not a major hindrance. Such hormonal therapy can sometimes also improve urinary obstructive symptoms, although not reliably so. Pretreatment hormonal therapy has also been promulgated by at least one group as a method for improving outcomes in less prognostically favorable groups of patients [11], although an improved outcome has not been reported by others [12].

Equipment and Planning Software

Equipment
Ultrasound unit with transducer
Needle templates
Software that projects the needle template pattern on the ultrasound display screen
Planning software
Packaged preplanning
Intraoperative planning

FIGURE 13-6. Ultrasound-based prostate brachytherapy systems are available as complete packages or can be obtained as individual components from various commercial sources. Components include an ultrasound unit with transducer, a holder-and-stepper unit for the transducer, needle templates, and software that projects the needle template pattern on the ultrasound display screen. It is essential that the alignment of the physical template relative to the software-projected template be checked to ensure that a needle inserted into a particular template hole does position accordingly on the display screen. It is also essential that the ultrasound unit be capable of obtaining sagittal (longitudinal) as well as the standard transverse images.

Many different packages of software for implant planning are available, either provided with the implant equipment or obtained separately. There are essentially two planning approaches: preplanning and intraoperative. In the preplanning mode, an ultrasound volume study of the prostate is acquired generally 1 week or more before the implant procedure and the data set is used to plan the location of seeds within the prostate. The implant is subsequently carried out as described later in this chapter. In an intraoperative planning mode, the images are acquired during the implant session and the planning software is used to plan seed locations immediately. Some commercially available software packages only have preplanning capabilities, whereas others can carry out both types of planning.

Ultrasound-based Prostate Volume Study

Determines prostate size
Acquires a data set used to determine the location and number of seeds needed to provide adequate dose coverage
Assesses pubic arch interference

FIGURE 13-7. Ultrasound-based prostate volume study. Planning for an implant requires that a transrectal ultrasound imaging data set be obtained of the prostate. Depending on whether preplanning or intraoperative planning is used, this ultrasound study is obtained either 1 week or more before or during the implant session itself. The ultrasound-based prostate volume study determines the prostate size and geometry to allow determination of the location, strength, and number of seeds necessary to cover the prostate with a suitable isodose line. In addition, the study permits an assessment of the likelihood of pubic arch interference.

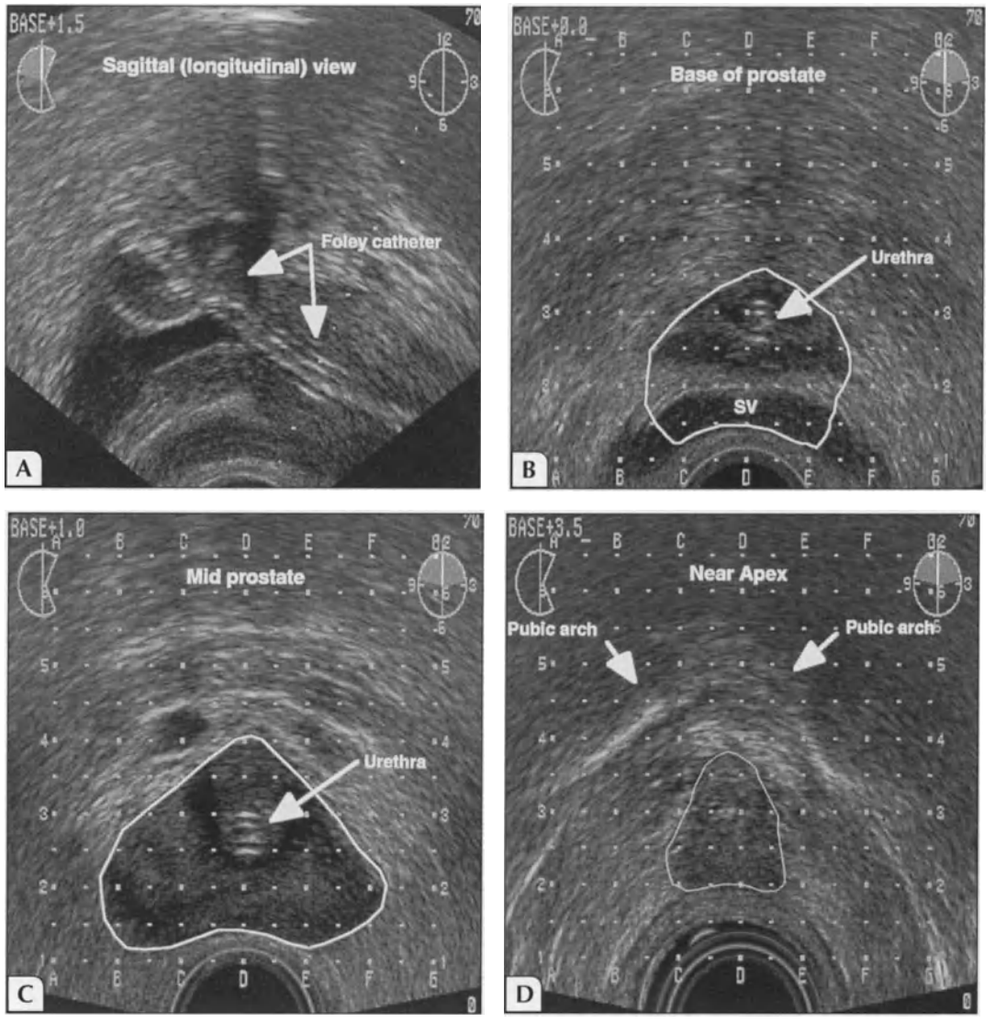

FIGURE 13-8. The patient is placed in a lithotomy position with femurs perpendicular to the table. Using a probe holder/stepper unit that is calibrated in 5-mm steps, a series of transverse images are obtained that cover the prostate from base to apex. Sagittal images (**A**) are also extremely useful in helping to better define the prostatic base and apex. It is generally best to have a modest probe angle with respect to the table, about a 5° to 10° tilt of the tip of the probe downward, because this better allows the probe to follow the posterior contour of the prostate along its length.

Several ultrasound planning images are shown. The ultrasound probe is initially positioned at the prostatic base (**B**), at which point one visualizes a portion of the seminal vesicles and the uppermost portion of the prostate. This probe position is termed the "base" with subsequent retractions in 0.5-cm steps labeled as +0.5, +1.0, +1.5, and so on. The upward (anterior) and pressure of the probe against the prostate is adjusted at midprostate (**C**) to have the bottom of the prostate several millimeters below one of the lower template rows, such as row "1" or "1.5" as shown. It is useful to visualize the urethra both during the planning volume study and the actual implant, to avoid placement of seeds in close proximity. This can be accomplished either by the injection of aerated gel or, as in the case here, by the presence of a 12-F Foley catheter. Larger catheters are not advisable because of the excessive ultrasound shadowing that they produce. Seeds should also not be planned for any positions directly anterior to the urethra, because a transperineal needle attempting to make a deposit in such a location would transect the urethra as it exits the apex of the prostate anteriorly (**D**).

The pubic arch can also be visualized to a satisfactory degree in these studies, as shown. It can be contoured at its narrowest point and the contour superimposed over the prostate at a point more cephalad where the prostate attains its widest dimension. This allows determination of the degree of shading. Thus, an ultrasound study can serve as a simple substitute for a more costly CT scan for determining whether the pubic arch will obstruct needle placement.

FIGURE 13-9. Implant planning. After an image data set spanning the entire prostate has been obtained, commercial software is used to plan seed positions to cover the entire prostate with a sufficient dose of radiation. This plan is carried out either preoperatively or intraoperatively depending on the approach used at the individual institution. Most practitioners also allow for a 2- to 5-mm extraprostatic margin, everywhere except at the prostatic-rectal interface, to both allow for potential imprecision in seed placement as well as to account for the possibility of extraprostatic extension of disease. As with the most recent dosimetric reevaluations, the current recommended minimum doses are 145 Gy and 110 Gy for ^{125}I and ^{103}Pd, respectively. When used as a brachytherapy boost in addition to external beam radiotherapy, recommended doses for these two isotopes are reduced to 75% or 80% of the above doses, respectively. Most seed-loading patterns are now planned according to a peripheral or modified peripheral schema to limit central prostatic and urethral doses to less than 125% to 200% of the prescription dose. Previously used uniform seed loading approaches appear to have led to higher urinary complications probably because of urethral overdosing.

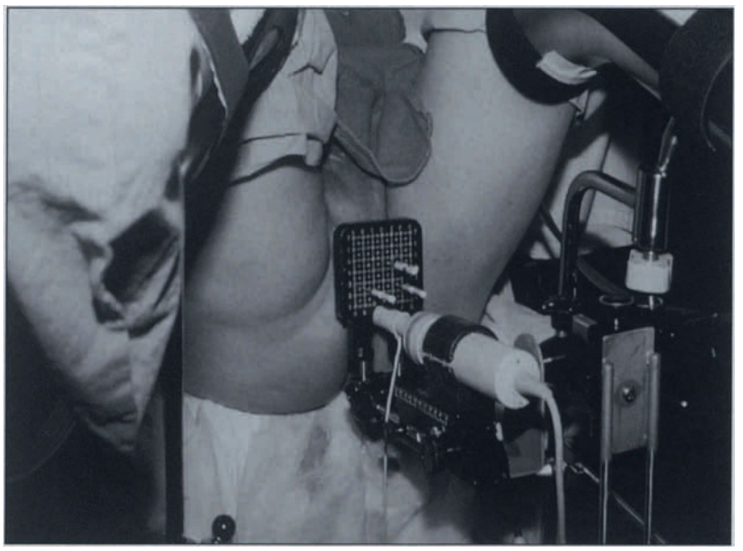

FIGURE 13-10. Prostate implantation. When using the preplanning method, the patient is subsequently brought back to the operating room and positioned to recreate as closely as possible the same position maintained during the volume study. Alternatively, if all planning is done intraoperatively, then the patient remains in the planning position and the implant proceeds. If preloaded needles are used, each needle will have been filled with the appropriate number of seeds, separated as necessary by absorbable suture spacers, to produce the calculated seed distribution along the template coordinates that needle will traverse. The tip of the needle is dipped into bone wax to prevent seeds from falling out of the open beveled tip of the needle. Before insertion of each needle, the ultrasound transducer is positioned at the level appropriate for that needle. Each implant needle is then inserted through the appropriate template hole until its tip is visualized on the ultrasound screen at the correct coordinate. If not correctly positioned, the needle is partially withdrawn, the bevel turned in the desired direction, and the needle reinserted. After the needle has been positioned correctly, bone wax is extruded by gentle pressure on the needle stylette until the first seed is positioned at the needle tip. The needle is then slowly withdrawn while the stylette hub is held stationary, leaving seeds and spacers in the predetermined locations along the needle track. Alternatively, a Mick applicator can be used to place seeds individually. In the case of intraoperative planning, during which there is no time for needle preloading, a Mick applicator is used instead. In general, the advantage of using a Mick applicator is a significant reduction in preparation time, because seeds need only be loaded into magazine cartridges. Conversely, however, use of preloaded needles substantially reduces intraoperative time.

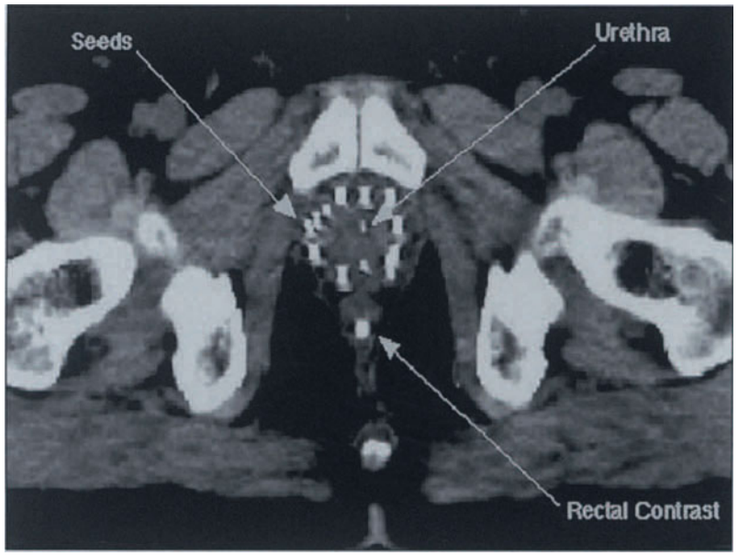

FIGURE 13-11. Postimplant evaluation. It is essential to evaluate the degree to which the actual implant matches the preimplant plan, both for purposes of identifying seriously suboptimal implants as well as to provide feedback to the clinician that will allow technical improvements. Postimplant evaluation is best achieved by CT imaging. The same planning software that is used for initial planning of an implant can generally be used for the postimplant analysis. Each seed position is digitized, isodose curves are generated, and the coverage of the prostate at different dose levels is assessed. Attempts have been made to correlate postimplant dosimetry with subsequent clinical outcome and indicate that, for ^{125}I, the 5-year biochemical control is excellent if at least 90% of the prostate volume receives at least 140 Gy [13].

OUTCOMES

Results of Studies on Permanent Seed Implants with or without EBRT

Study	*Isotope*	*Patients, n*	*PSA Control, %*	*Follow-up, y*
Grimm *et al.* [14]	^{125}I	125	85.1	10
Beyer and Brachman [15]	^{125}I	695	71	5
Ragde *et al.* [16]	^{125}I	147	66	10
Grado *et al.* [17]	$^{125}I/^{103}Pd$±EB	490	79	5
Stock and Stone [18]	$^{25}I/^{103}Pd$	258	75 (PSA < 20)	4
Zelefsky *et al.* [19]	^{125}I	248	71	5
Critz *et al.* [20]	^{125}I + EB	689	88	5
Blasko *et al.* [7]	$^{125}I/^{103}Pd$±EB	634	85	10

FIGURE 13-12. Outcomes of several series that contained large numbers of patients treated with permanent seed implants with or without external beam radiotherapy (EBRT). The criteria for prostate-specific antigen (PSA) control used by various authors differ and may influence the calculated disease control rates, although there is a tendency for these variously calculated rates to become fairly equivalent with increasing follow-up. In addition, the control rates noted here are for the total patient groups treated, which, although consisting of mostly prognostically favorable patients, did in most studies also include patients with unfavorable PSAs or tumor grades. In general, when grouped according to pretreatment PSA or grade, those patients presenting with PSAs less than 10 ng/mL and Gleason scores 6 or lower had substantially higher PSA control rates than the total group averages listed in this figure.

COMPLICATIONS

Complications

Complication	*Approximate Frequency, %*
Urinary	>90 (40 grade 2)
Acute urethritis	3–7
Prolonged urethritis	5
Acute obstruction, (catheter)	5
Prolonged obstruction	5
Proctitis (limited bleeding)	25–50 depending on the age at treatment
Erectile dysfunction	

FIGURE 13-13. Nearly all patients experience a degree of prostatitis and urethritis as well as some degree of obstructive symptomatology during the first 1 or 2 months after a permanent implant. Very early symptoms are likely to be related to prostatic swelling secondary to the trauma of the implant, whereas subsequent symptoms probably relate more to radiation effects. Nearly half of patients benefit from the use of α-blockers. Nonsteroidal anti-inflammatory drugs can also be of benefit sometimes. As is the case with external beam radiotherapy, the risk of erectile dysfunction varies with the age of the patient at the time of implant and appears to be numerically similar to rates observed after external beam treatment. In a properly performed implant, radiation proctitis with bleeding occurs only rarely and is generally self-limiting.

HIGH DOSE–RATE TEMPORARY PROSTATE IMPLANTS

Results of Studies on High Dose–Rate Temporary Prostate Implants

Study	*Patients, n*	*Risk Group*	*PSA Control, % (y)*	*Follow-up, mo*
Kestin *et al.* [21]	161	Intermediate–high	67 (5)	30
Mate *et al.* [22]	104	Low, intermediate, high	100 (5)	76
			78 (5)	—
			44 (5)	—
Galalae *et al.* [23]	144	Variable	72.9 (8)	96

FIGURE 13-14. Results of studies on high dose–rate (HDR) temporary prostate implants. Afterloading machines that use an ^{192}Ir source have provided an alternate approach for the delivery of brachytherapy to various anatomic sites including the prostate. In the case of prostate cancer, such treatment has generally been used as a boost in combination with external beam radiotherapy [21–23], although more recently reported efforts have documented the potential feasibility of using only this approach [24,25]. Perhaps the major advantage of the method is in using the ability of the afterloading machine to drive the radioactive source sequentially through the needles of an array placed transperineally under ultrasound guidance into the prostate. These machines can be programmed to allow the source to dwell for different lengths of time at various positions within each needle to produce a composite radiation isodose distribution that ultimately encompasses the prostate while delivering minimal doses to surrounding structures.

Large fraction sizes ranging from 4 to 9.5 Gy each have been used at various institutions. Such large fraction sizes may be advantageous given the emerging evidence that prostate cancers have a very high capacity to repair radiation damage between radiation fractions, perhaps higher than in most normal tissues [9,26]. Under these circumstances, a large dose for session would preferentially suppress repair of radiation injury in the prostate tumor and lead to a higher ratio of tumor control to normal tissue toxicity.

Outcomes to date suggest that the combination of external beam radiation and HDR boost are at least equivalent to other radiation therapy approaches in tumor control rates and toxicities. Early results from HDR monotherapy trials suggest acceptably low levels of morbidity, although longer follow-up is needed to assess the tumor control efficacy of this approach [27,28].

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14

Cryoablation of Prostate Cancer

Katsuto Shinohara
& Peter R. Carroll

The incidence of prostate cancer has more than doubled since the late 1980s, and 184,500 new cases will be detected this year. This increase is largely due to increased use of prostate-specific antigen (PSA)-based screening, transrectal ultrasonography, and random biopsy of the prostate. The treatment of prostate cancer, however, remains controversial. No consensus has been established as to what constitutes appropriate treatment for any stage of disease, especially for localized cancers. Radical prostatectomy, radiation therapy, and watchful waiting all have been proposed, and their risks and benefits are frequently discussed. Radical prostatectomy has been criticized for its perceived high morbidity [1], whereas radiation therapy has been criticized for its uncertain efficacy [2]. Such criticisms of the conventional treatments have stimulated a search by patients and physicians for alternative treatments that may be both effective and associated with limited morbidity.

Cryosurgical ablation of the prostate was first attempted using an open technique, leading to high failure rates and significant side effects [3–6]. Improved percutaneous techniques, expertise in transrectal ultrasound, new cryotechnology, and better understanding of cryobiology have created a renewed interest in cryosurgical ablation of prostate cancer [7].

History of Cryosurgery for the Prostate Gland

Study (year)	*Procedure*
Gonder *et al.* [3] (1964)	Transurethral cryogenic prostatectomy for bladder outlet obstruction
Flocks *et al.* [4] (1969)	Transperineal open cryosurgery for prostate cancer
Reuter [5] (1972)	Transperineal trocar cryoablation for prostate cancer
Bonney *et al.* [6] (1982)	Transperineal open cryosurgery for prostate cancer follow-up results
Onik *et al.* [8] (1993)	Transperineal percutaneous ultrasound-guided cryoablation for prostate cancer

FIGURE 14-1. Background. The first description of cryoablation of the prostate was published in 1966 [3]. Shortly thereafter, an attempt to destroy prostate cancer using a transperineally introduced probe was reported [5]. In 1969, urologists at the University of Iowa reported their experience with the transperineal approach [4]. Outcome, in terms of survival and recurrence, was related to stage and grade; about 41% of patients eventually had evidence of persistent or recurrent disease. Although the technique compared favorably with other treatment modalities with respect to survival, morbidity was significant. Urethral sloughing of tissue was common. Urethrorectal or urethrocutaneous fistulas developed in 13% of patients, bladder neck obstruction developed in 2.3%, and urinary incontinence developed in 6.5% [6]. This early experience was recently reviewed. Cancer recurrence was documented in 78.4% of the men, and 47.1% died of prostate cancer. Local recurrence was documented in at least 67% of those undergoing the procedure. Kaplan-Meier analyses demonstrated median progression-free and overall survival times of 34 and 75 months, respectively [7].

Despite the discouraging early results, enthusiasm for finding a minimally invasive alternative therapy for prostate cancer led to refinements in the technique of cryoablation. In 1993, Onik *et al.* [8] first reported the currently used technique of percutaneous transperineal ultrasound-guided cryoablation.

CRYOBIOLOGY

Mechanism of Cryogenic Tissue Ablation

Direct effect on cells
- Extracellular crystal formation leading to cellular dehydration
- pH change due to abnormal electrolyte concentration leading to denature of cellular proteins
- Thermal shock with damage to lipoproteins
- Mechanical cellular membrane disruption by intracellular crystallization
- Cellular swelling due to fluid shift during thawing

Vascular stasis due to thrombosis after freezing

FIGURE 14-2. Biological mechanisms of tissue destruction. Cellular damage during freezing is the result of many mechanisms. Once the extracellular fluid reaches a tissue temperature of less than 0°C, it starts to crystallize. This increases the osmotic pressure of the unfrozen portion of the extracellular fluid compartment, leading to water shifting from the intracellular space to the extracellular space. As a result, cells become dehydrated. Cellular pH also changes, leading to denaturing of cellular proteins [9]. With further temperature drops, water in the intracellular space crystallizes. This mechanically breaks the cellular membrane. On thawing, extracellular fluid shifts back again into the intracellular space, leading to cellular bursting.

The blood vessels around the targeted tissue initially dilate after thawing. Hyperpermeability of the vessel wall occurs. After a few hours of this hyperemic state, microthrombi form on the damaged vessel wall, leading to ischemia of the tissue [10].

Tissue damage occurs, therefore, during both freezing and thawing. Both the duration and the number of freeze:thaw cycles are correlated with the extent of cell death. Once the tissue has reached a steady state of very low temperature, the duration of freezing appears to have little effect on tissue damage. It is known that repeating the freeze:thaw cycle creates a larger area of tissue damage, even though the low temperature achieved on each cycle is the same [11]. Cells that remain viable after the initial cycle are damaged on the second or third freeze:thaw cycle. The velocity of the temperature change also affects the extent of tissue damage. Faster freezing appears to cause more tissue damage than do slow temperature changes.

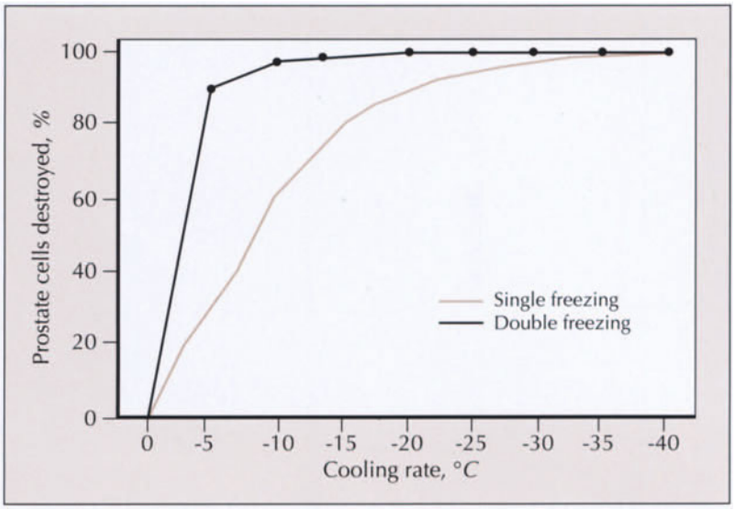

FIGURE 14-3. Single freeze versus double freeze. Repeated freeze:thaw cycles create more extensive tissue damage than does a single cycle [11]. Tatsutani *et al.* [12] analyzed these effects in vitro using prostate cancer cell lines treated with various temperatures, speeds of freezing, and numbers of freeze:thaw cycles. They showed that cancer cells are not completely destroyed with a single freeze:thaw cycle to -40°C. However, cells are completely destroyed at -15°C if two freeze:thaw cycles are used [12]. (*Adapted from* Tatsutani *et al.* [12].)

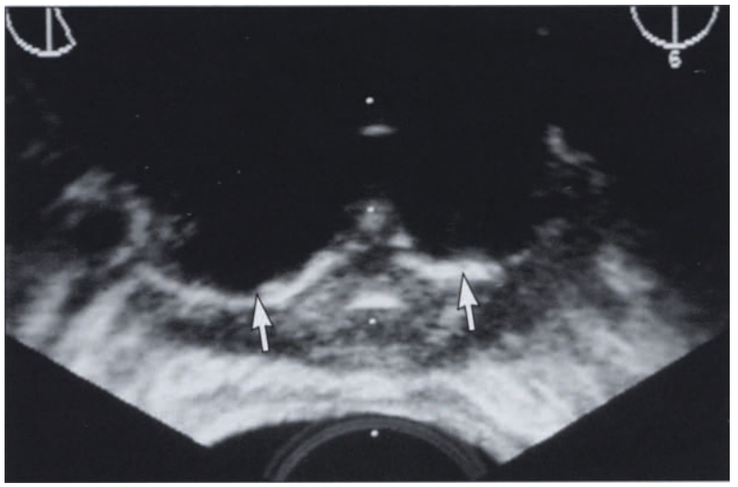

FIGURE 14-4. Ultrasound image of frozen tissue. In this transverse sectional transrectal ultrasound image of the prostate gland during cryosurgery, the edge of the ice ball is seen as a highly echogenic line with acoustic shadows behind it (*arrows*). Because the sound impedance drastically changes from the frozen tissue to the unfrozen tissue, most of the sound waves are reflected at the interface, creating the strong acoustic shadow. Beyond this interface, nothing can be monitored by ultrasound because of this artifact. The temperature at the leading edge of ice is approximately 0°C.

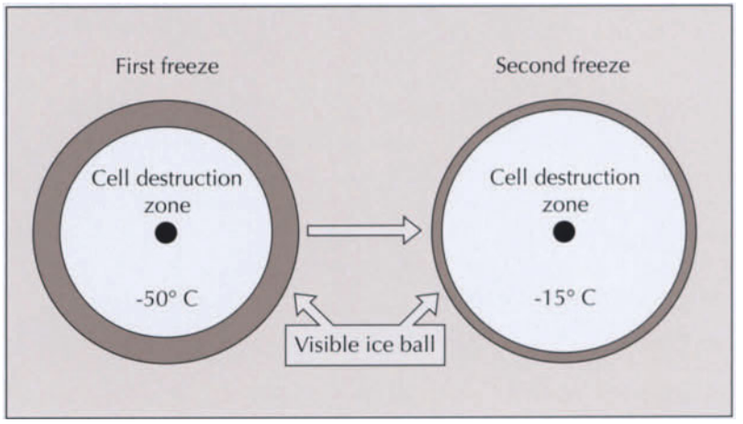

FIGURE 14-5. Frozen zone and tissue destruction zones. Complete cell death occurs in the area with temperature of -40°C or less, which is several millimeters inside the leading edge of the freezing zone (*left*). Therefore, completely covering the prostate with the ice ball does not guarantee complete cell death. It is necessary to extend the iceball beyond the edge of the prostate to ensure adequate tissue ablation at the edge of the prostate. On the second freeze:thaw cycle, the zone of tissue destruction comes closer to the edge of the iceball (*right*), based on the mechanism discribed in Figure 14-2. Two freeze:thaw cycles are used routinely in areas of prostate cancer to ensure adequate tissue destruction.

EQUIPMENT

A. Currently Available Cryosurgical Devices for Use in the Prostate Gland

	Source of Freezing	*Gas Recycle?*	*Cooling Temperature*	*Maximum Number of Probes*
CMS	Liquid nitrogen	Yes	-195°C	5
Candela	Liquid nitrogen	No	-186°C	5
Endocare	Liquid argon	No	-130°C	8

FIGURE 14-6. Cryogenic equipment. **A** and **B**, Three cryosurgical devices for prostate cancer treatment are available in the United States. The Candela (Wayland, MA) system is a liquid nitrogen–based machine; the liquid nitrogen evaporates at the tip of the probe, leading to its cooling. Liquid nitrogen is not reused. The CMS (Rockville, MD) system uses ultracooled liquid nitrogen; the nitrogen is compressed and cooled to -206°C. At this temperature, liquid nitrogen becomes partly frozen (slush). This cools tissue down to approximately -185°C. Liquid nitrogen is reused in this system [13]. The Endocare (Irvine, CA) system uses liquid argon as the source of freezing. The Candela and CMS systems can freeze up to five probes simultaneously; the Endocare system can freeze up to eight probes.

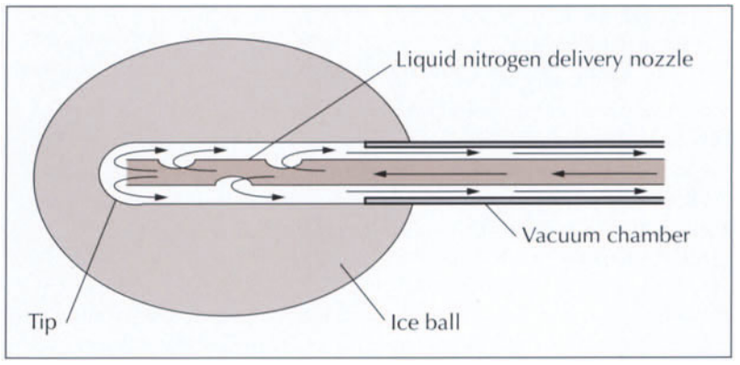

FIGURE 14-7. Structure of the cryoprobe. The CMS cryoprobe is 3 mm in diameter and has a double lumen. Ultracooled liquid nitrogen is delivered through a thin lumen to the tip of the probe. Partially evaporated liquid nitrogen returns through the outer chamber, just underneath the surface of the probe. The shaft and base of the probe are insulated with a vacuum chamber to protect normal tissue from freezing.

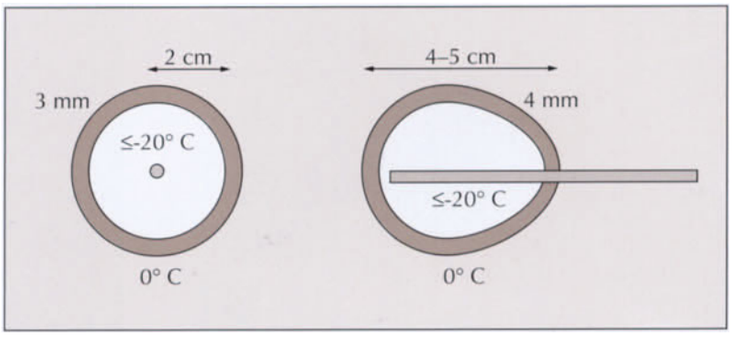

FIGURE 14-8. Ice ball structure. An ideal cryosurgical device should create smoothly outlined and symmetrical ice formation around the probe. To destroy the tissue successfully, the temperature gradient around the probe should be steep, with a rapid temperature drop within a few millimeters of the surface. The probe temperature, therefore, should be very low. The ice-ball formed at the tip is elliptical in shape, with a maximal diameter of approximately 2 cm at the tip of the cryoprobe. The ice ball is about 4 to 5 cm in length [14].

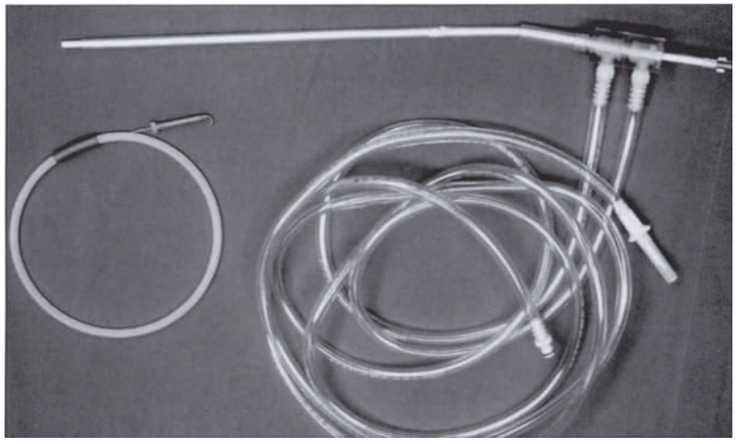

FIGURE 14-9. Urethral warmer. The urethral warmer is a flexible, double-lumen catheter through which warmed saline can be irrigated continuously at a high flow. The catheter surface is made of a thin membrane that conducts heat very well [15]. Use of an effective urethral warming device is essential to reduce the incidence of complications associated with cryoablation, such as tissue sloughing, stricture formation, and urinary incontinence.

PATIENT SELECTION

Conditions Suitable for Treatment with Cryoablation

Localized cancer confined within the gland (T1–2)
Localized cancer with extraprostatic extension (T3–4)
Local recurrence after radiation therapy
Local recurrence after radical prostatectomy
Local recurrence after cryoablation
Local tumor progression after hormone therapy

FIGURE 14-10. Treatable prostate cancers. Cryoablation is associated with a very low operative risk. It usually can be done as an outpatient procedure, and no transfusion is required. This procedure has been used to treat not only localized disease, but also regionally extensive disease and cancers that have recurred after radiation and radical prostatectomy. Patients who have been treated previously with cryoablation and have had local recurrence of disease are candidates for repeat cryoablation. However, the patients most likely to respond favorably, showing low and stable posttreatment serum prostate-specific antigen (PSA) and negative biopsy, are those with localized prostate cancers.

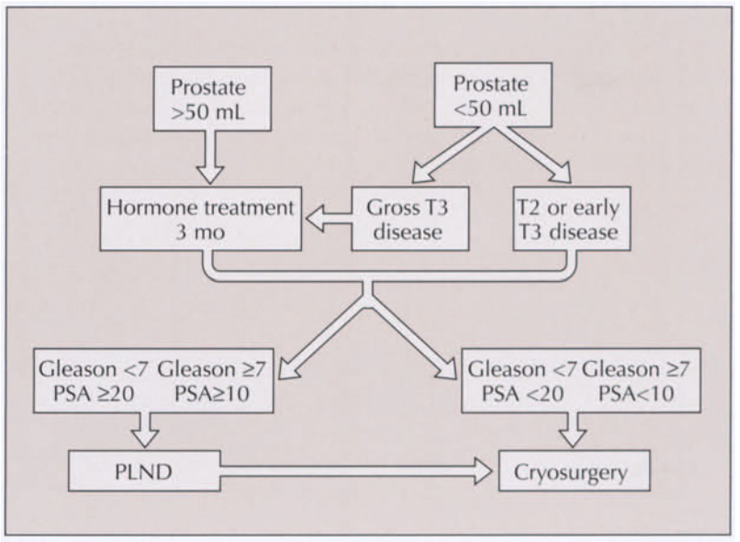

FIGURE 14-11. Preoperative considerations. Patients with gross extracapsular extension or seminal vesicle invasion are treated with neoadjuvant hormone therapy to reduce the tumor volume and allow for easier inclusion within the iceball. If the prostate is larger than 50 cm^3, complete freezing of the prostate with a limited number of probes becomes difficult. In these patients, neoadjuvant hormone therapy also is indicated. Patients with a high likelihood of lymph node metastases (*ie*, Gleason grade ≥ 7 with prostate-specific antigen [PSA] > 10 or Gleason grade ≤ 6 but PSA > 20) are advised to undergo simultaneous pelvic lymph node dissection (PLND). This can be carried out through a small incision ("mini-lap") in the suprapubic area. Patients undergo light bowel preparation consisting of oral magnesium citrate the day before the procedure and a Fleet enema the morning of the procedure.

PROCEDURE

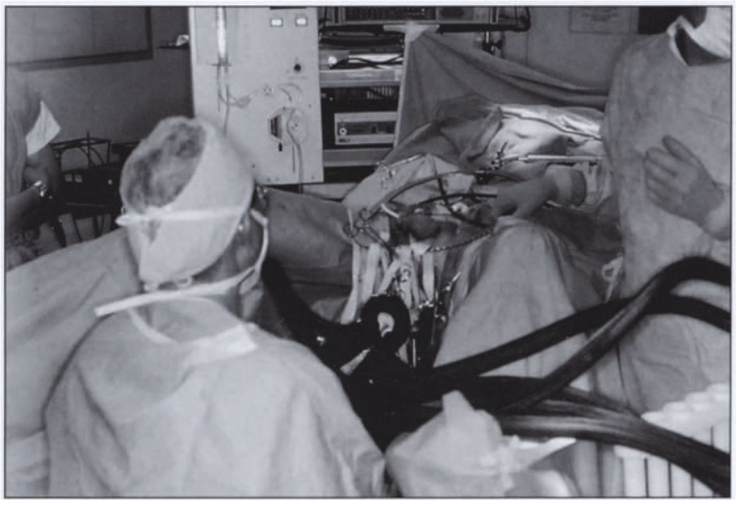

FIGURE 14-12. Patient positioning. After induction of regional or general anesthesia, the patient is placed in the lithotomy position. A Foley catheter is inserted, and the bladder is distended with saline to prevent the intraperitoneal contents from being close to the freezing area. Before freezing, the Foley catheter is removed and replaced with the urethral warmer, and irrigation of the catheter with warm saline is begun. The cryoprobes are placed transperineally under ultrasound guidance.

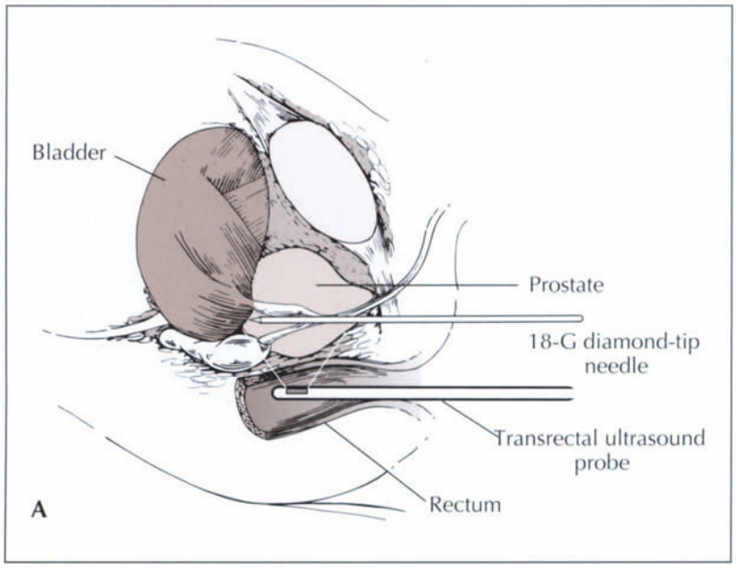

FIGURE 14-13. Needle insertion. **A**, Using a perineal needle insertion guide, an 18-gauge, diamond-tipped, hollow-core needle is inserted into the prostate under ultrasound guidance.

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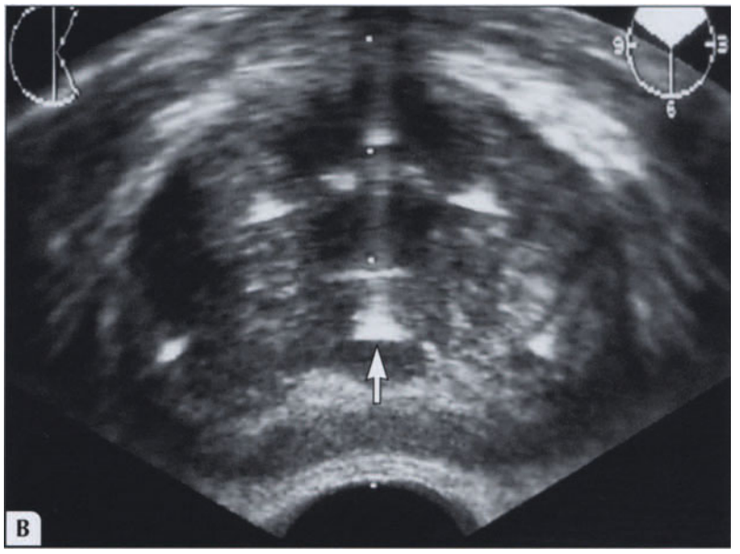
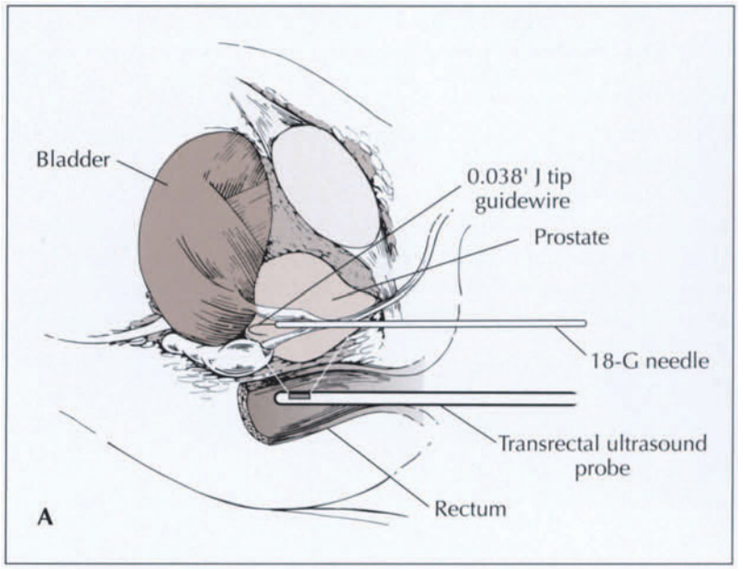


FIGURE 14-13. (***Continued***) The needle locations are seen as bright dots on ultrasound imaging (**B**, *arrow*). The exact positioning of each needle and resulting probe is determined at this point. Each needle is advanced up to the desired location, usually up to the base of the prostate. Usually five to six needles are inserted, two anteromedially, two posterolaterally, and one or two posteriorly.



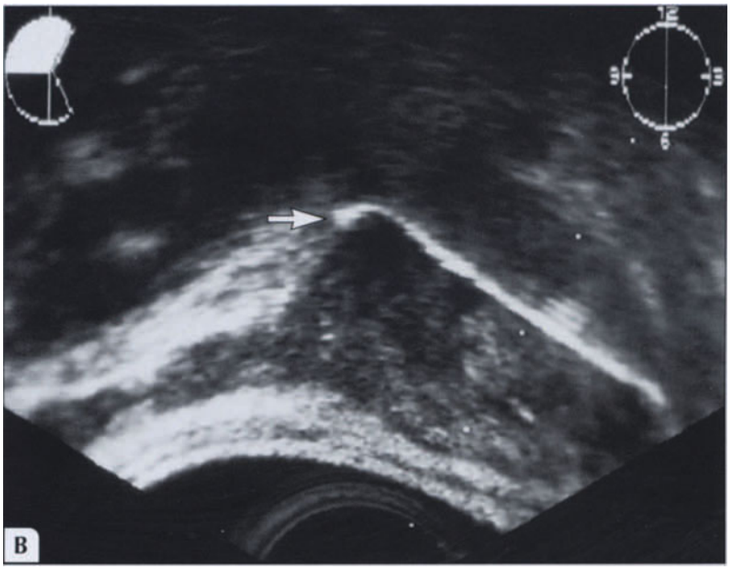


FIGURE 14-14. J guidewire placement. **A**, Once the needle is in position, a 0.038-in J tip guidewire is advanced through the needle to the proximal extent of the prostatic capsule. **B**, Sagittal view of the prostate gland shows the correct placement of the guidewire (*arrow*). The needle is removed after confirming that the guidewire is in position.

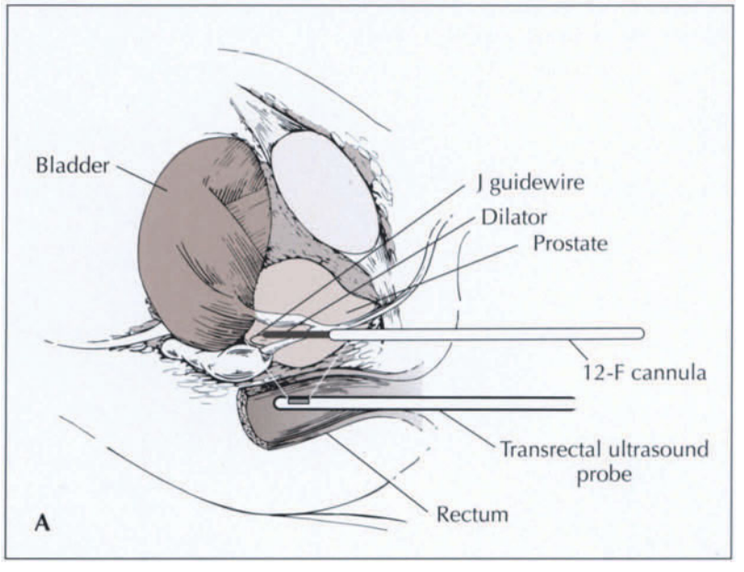


FIGURE 14-15. Dilator and cannula placement. **A**, Dilators followed by 12-F cannulas are inserted into the prostate over the guidewires. The cannula is positioned against the proximal extent of the capsule, and both wire and dilator are removed.

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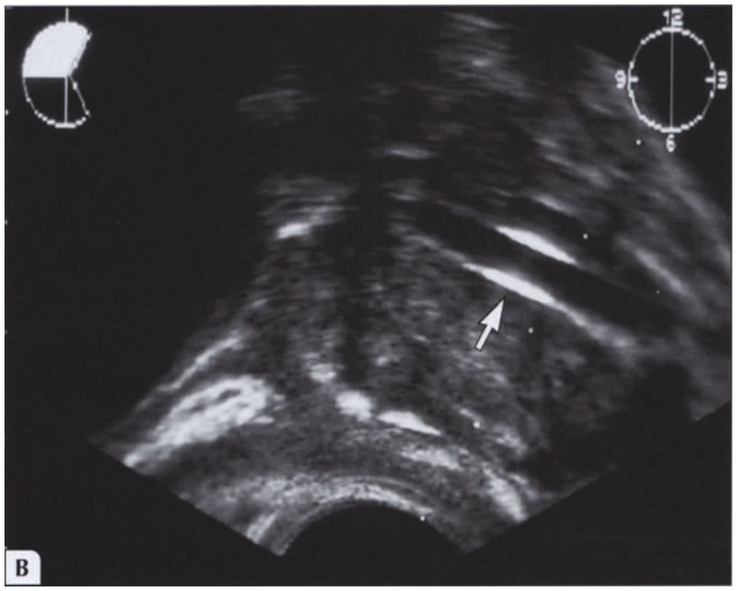
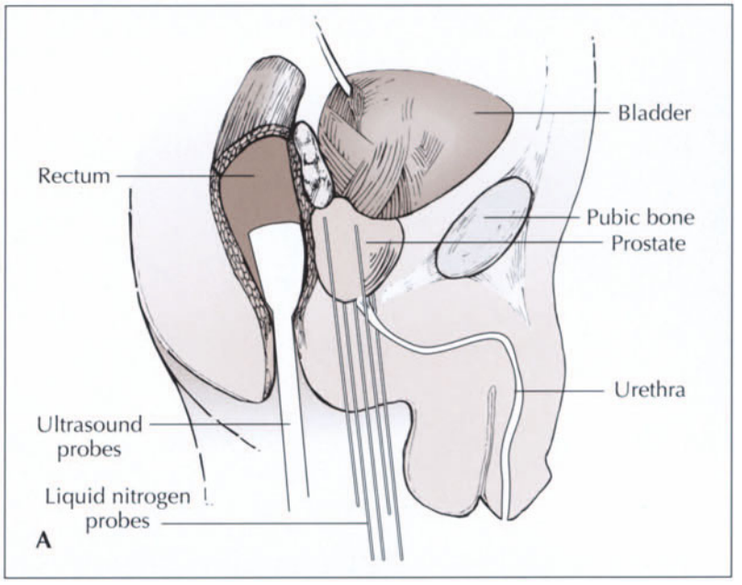
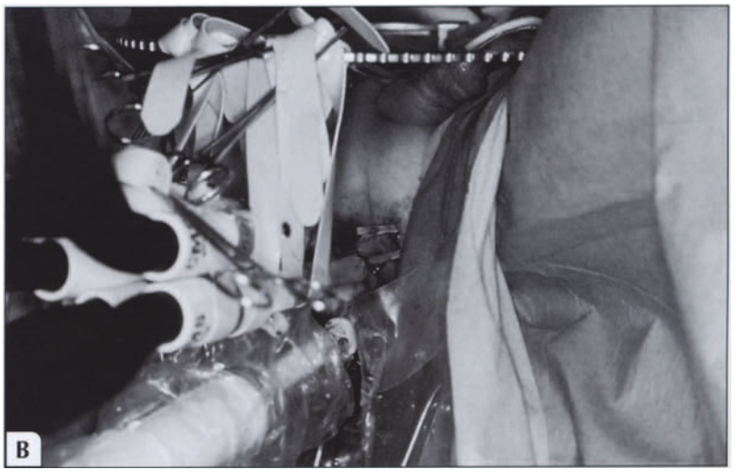


FIGURE 14-15. (***Continued***) **B,** Sagittal view of the prostate confirming correct positioning of the cannula (*arrow*).





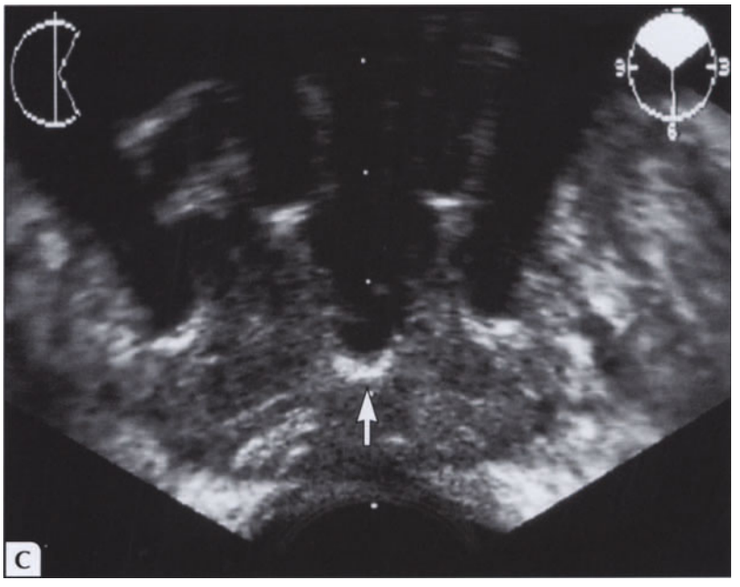
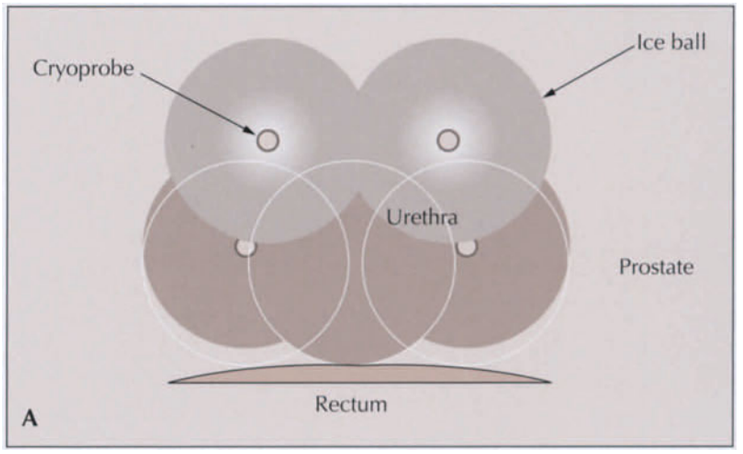


FIGURE 14-16. Placement of cryoprobes. Before placement of the cryoprobes, the urethral warmer must be in position and irrigation with warm saline must be started. **A,** The cryoprobes are placed and the cannulas are retracted to expose the tip of the probe. **B,** Five probes are usually placed: two anteromedially and three posteriorly. Six to eight additional probes may be used to achieve more conformal freezing of the prostate gland. **C,** The probes are secured in position by freezing each probe to -70°C ("stick" temperature). This creates a small ice ball around the tip of the probe (*arrow*).



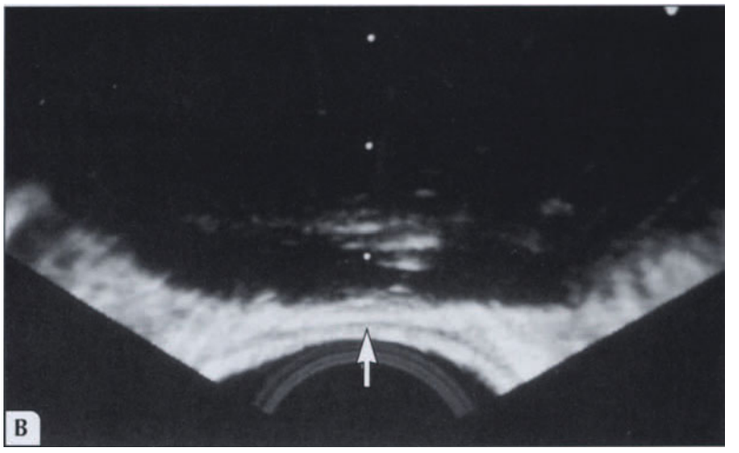
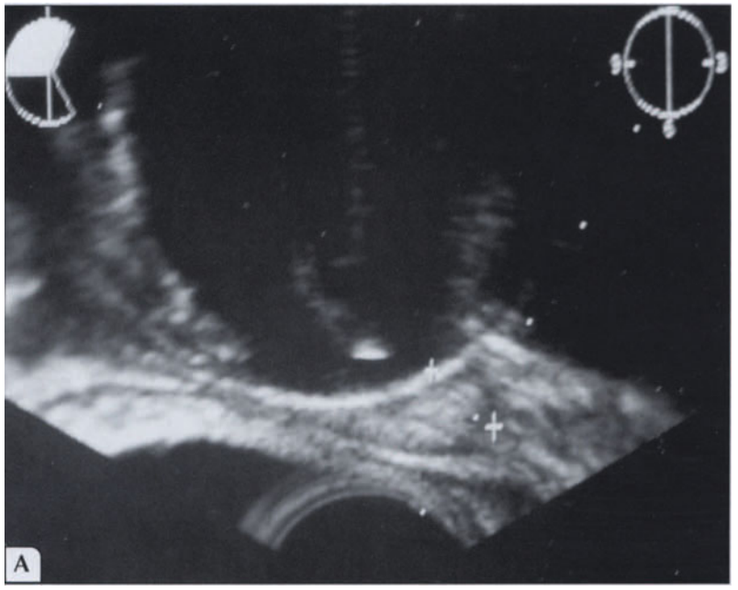


FIGURE 14-17. Freezing from the anterior portion of the prostate gland. Liquid nitrogen is circulated through the anterior probes, and the resulting freezing zones or "iceballs" are monitored by ultrasound (**A**). Once ice is formed inside the prostate, everything anterior to the ice is hidden by the acoustic shadow. Therefore, the anterior probes must be activated first. The iceball is allowed to extend posteriorly and laterally. **B**, Once these have reached the desired positions thawing is begun and the posterior probes are activated (*arrow*). The posterior iceballs are allowed to extend to the muscularis propria of the rectal wall. Freezing beyond this may result in damage to the rectum and development of a rectourethral fistula.



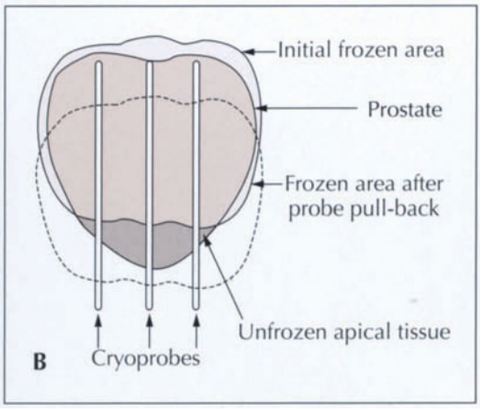
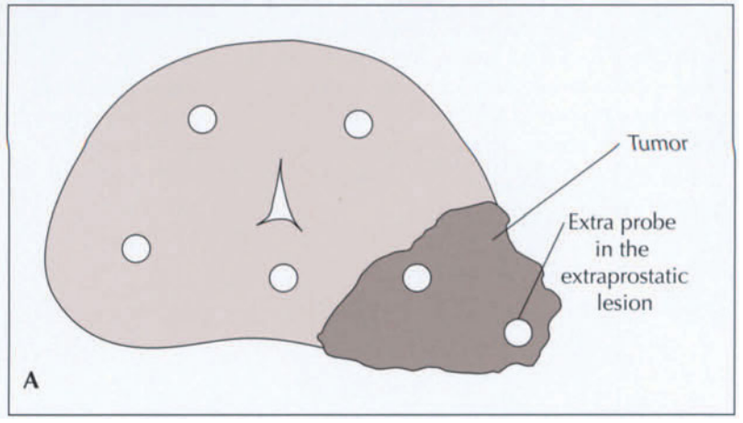


FIGURE 14-18. Unfrozen apical tissue. Most surgeons routinely perform two freeze:thaw cycles. **A**, If the iceball does not extend adequately to the apex of the prostate the cryoprobes are pulled backward into the apex and additional freezing is carried out (**B**). The use of two freeze:thaw cycles is more likely to result in complete cancer ablation than is the use of a single cycle, as stated previously.



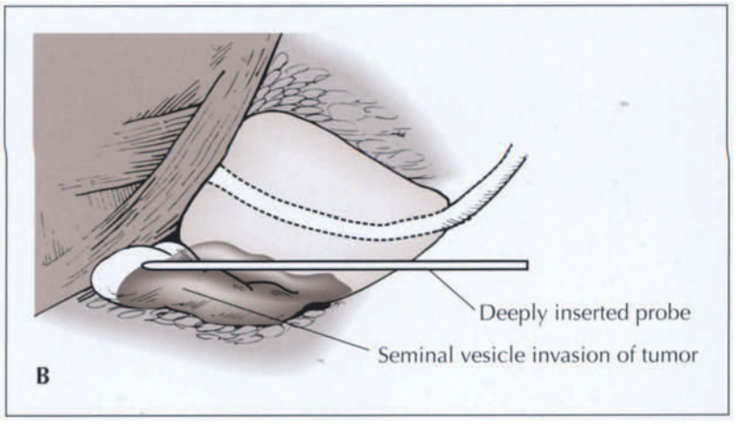


FIGURE 14-19. Freezing of extraprostatic lesions. To ensure adequate treatment of cancer, the iceball often is allowed to extend 2 to 4 mm laterally into the periprostatic tissues, 6 mm beyond the apex and into the muscularis propria of the rectum posteriorly. In areas of extracapsular cancer extension, greater propagation of the freeze zone is permitted laterally. **A**, If necessary, an additional probe may be placed in such areas. **B**, When seminal vesicle invasion is present, probes must be placed deep into the seminal vesicles.

Complications Associated with Cryoablation of the Prostate Gland

	Incidence of Complications, %	
	Mixed Cases	*Radiation Failure*
Tissue slough	15.4	22
Urinary retention	2.9–23.0	27.0–40.9
Stricture	4.0–7.0	2–33
Incontinence	2.0–8.5	9–95.5
Impotence	20–84	72–100
Pelvic or rectal pain	0–5	8.0–40.9
Penile numbness	0.5–10.0	22
Rectourethral fistula	0–4	0–11
Hydronephrosis	0	0–36.4

FIGURE 14-20. Complications associated with prostate cryosurgery. Various complications have been reported after cryoablation of the prostate. These complications are caused mainly by freezing of the normal surrounding tissue, such as the urethra, sphincter, pelvic musculature, rectum, and ureter. These complications usually are not apparent initially, but are noted 2 to 3 weeks after the procedure. Common complications include tissue sloughing, pelvic pain, and impotence. Rectourethral fistulas are rare.

Patients treated after radiation therapy have significantly higher numbers of complications and morbidity than do those who have not had such previous treatment. Lee *et al.* [16] reported that incidences of rectourethral fistula and total incontinence after cryosurgery were 0.33% for patients who had not received radiation, but were 8.7% for those patients who had been treated previously with radiation. (*Data from* Lee *et al.* [14], Lee *et al.* [16], Bahn *et al.* [17], Patel *et al.* [18], Miller *et al.* [19], Coogan and McKiel [20], Bales *et al.* [21], Weider *et al.* [22], Shinohara *et al.* [23], Pisters *et al.* [24], and de laTaille *et al.* [25].)

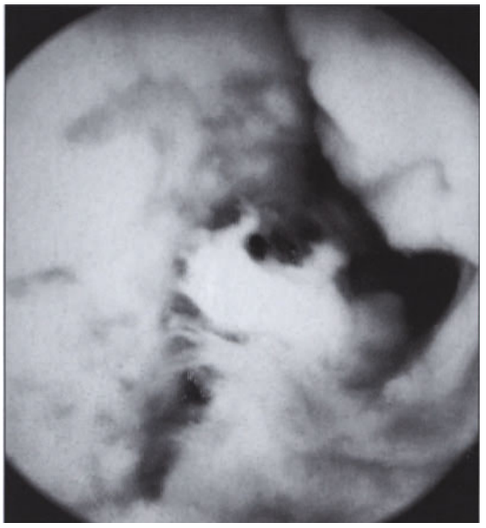


FIGURE 14-21. Tissue sloughing requiring transurethral resection. Formerly, one of the more common complications of cryosurgery was tissue sloughing, caused by inadequate urethral protection from freezing and, possibly, infection of the frozen tissue. Cystoscopy revealed soft necrotic prostatic tissue occluding the prostatic urethra. Tissue slough often was associated with urinary tract infection. Infection of the sloughed tissue was not always symptomatic. Transurethral resection often was necessary to remove the obstructing sloughed tissue. Formation of both strictures and stones occurred as a result of urethral damage in some patients. There was a significant relationship between the incidence of tissue sloughing and the type of urethral warmer used (see Fig. 14-9). The incidence of this complication has decreased significantly as a result of routine use of an effective urethral warmer and the practice of leaving a urethral catheter in place for 2 or 3 weeks after the procedure.

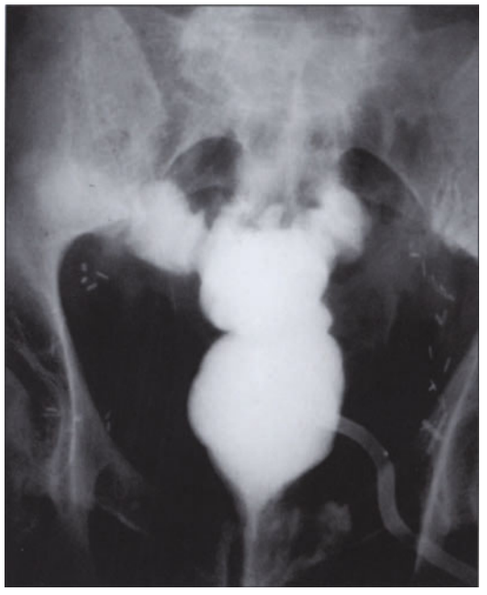


FIGURE 14-22. Rectourethral fistula formation. Rectourethral fistulas are rare, but the complication is difficult to treat when it occurs. Fistulas are more likely to develop in patients who have received radiation. Patients with this complication report watery stools consistent with leakage of urine into the rectum. A cystogram or CT scan confirms the diagnosis and location of the fistula. This voiding cystogram shows radiocontrast medium leaking into the rectum and sigmoid colon. Conservative treatment with a Foley catheter or a suprapubic catheter rarely results in complete healing of the fistula, although it should be performed initially. The tissue around the fistula is necrotic, and at least 6 months of tissue healing is necessary before operative repair of the fistula can be done. During this period, diversion of urine using a catheter is advisable. Both transperineal and transrectal approaches to repair have been used with high success rates.

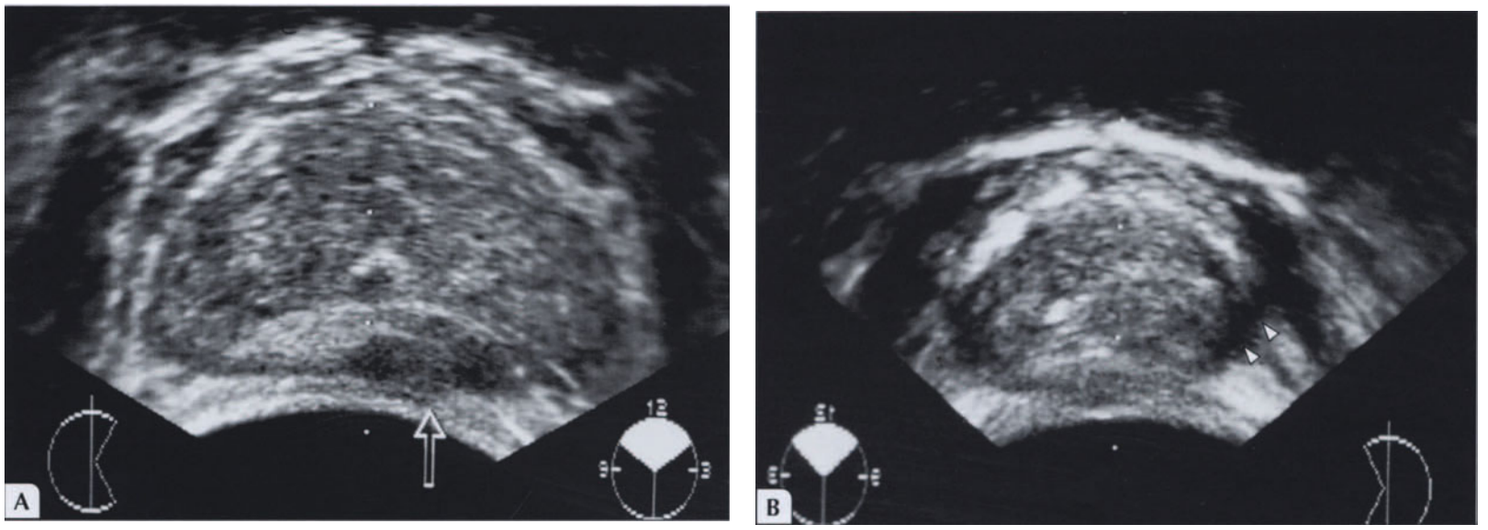


FIGURE 14-23. Transrectal ultrasound images before and after treatment. **A,** Transverse, transrectal ultrasound view of a localized prostate cancer before cryoablation. A hypoechoic area representing the cancer is seen in the left peripheral zone (*arrow*). **B,** Six months after cryoablation, the prostate is significantly smaller with rather heterogeneous echogenicity and lack of delineation of the internal anatomy. **B,** The prostate boundary is obscured because of complete freezing of the gland up to and including the prostatic capsule (*arrowheads*). The hypoechoic area seen on preoperative ultrasonography is no longer visible.

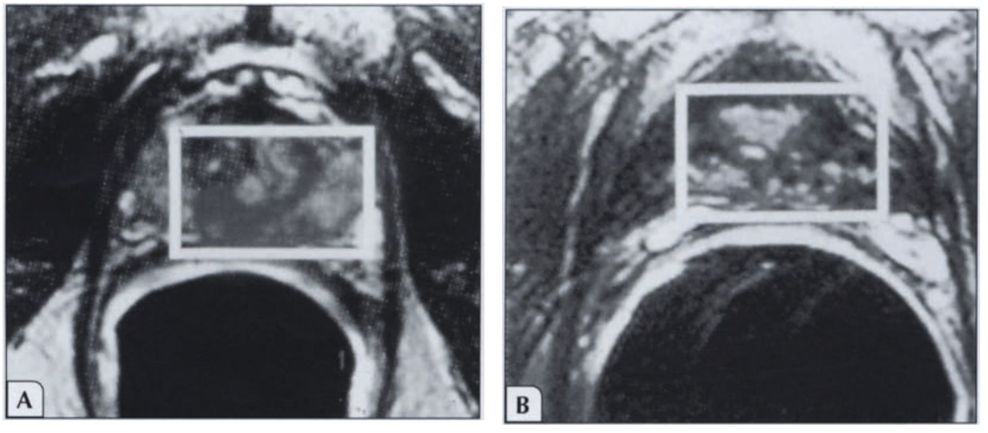


FIGURE 14-24. ***(See Color Plate)*** Magnetic resonance imaging and spectroscopy after cryoablation of the prostate. Cancer tissue has higher choline and lower citrate levels than does benign prostate tissue. Magnetic resonance spectroscopy of the prostate performed preoperatively shows tissue with abnormal choline: citrate signal ratios corresponding with a biopsy-proven prostate cancer (**A**, *red area*). **B**, After successful cryosurgery, all signals in the prostate disappear, indicating total necrosis of the gland [26].

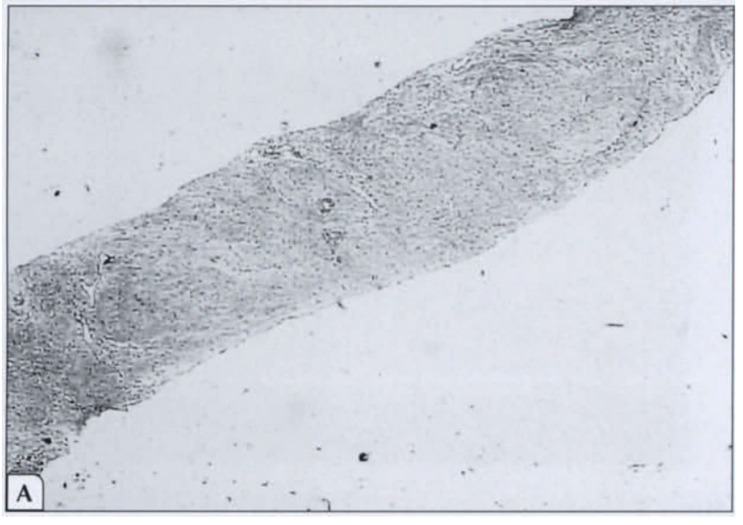


FIGURE 14-25. Biopsy of the prostate after cryoablation. **A,** Biopsy of the prostate reveals fibrous stroma tissue with complete disappearance of glandular tissue.

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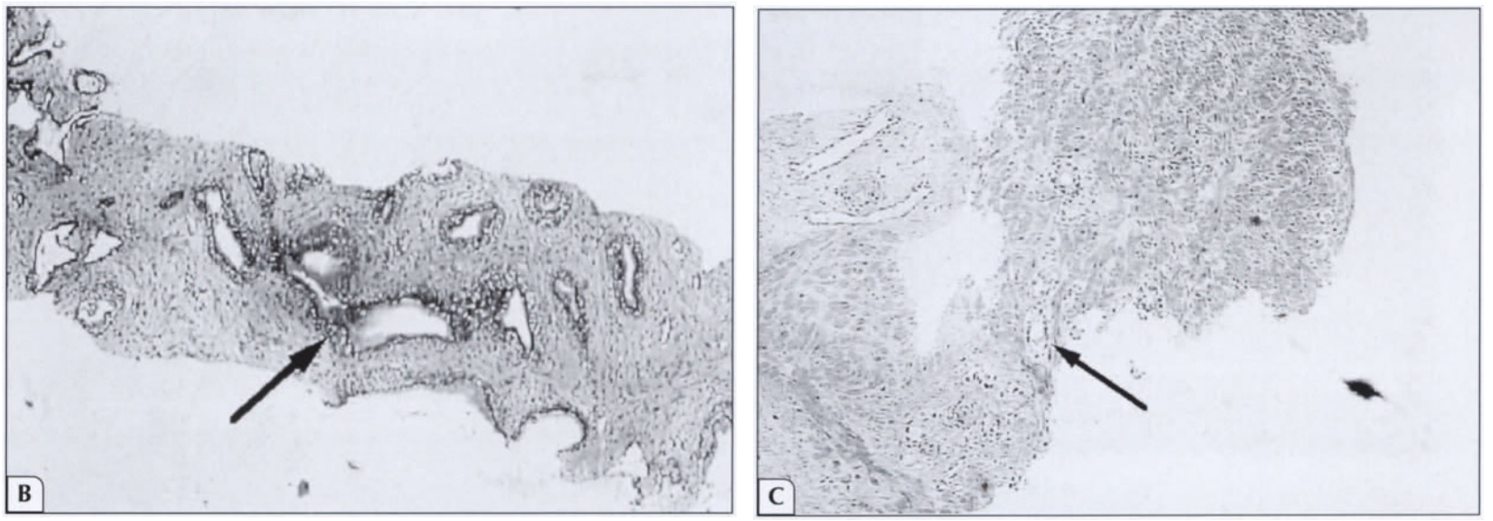

FIGURE 14-25. (***Continued***) **B,** Occasional glandular structures (*arrow*) can be seen. These glands may represent either residual prostate tissue around the urethra or regrowth of prostatic duct epithelium in the area of treatment (basal cell hyperplasia). **C,** Residual cancer (*arrow*) is seen more commonly in the apex of the prostate and in the seminal vesicles (see Fig. 14-27). Residual cancer may be found in the periurethral region and around large vessels, where temperatures may be higher than in the surrounding tissues.

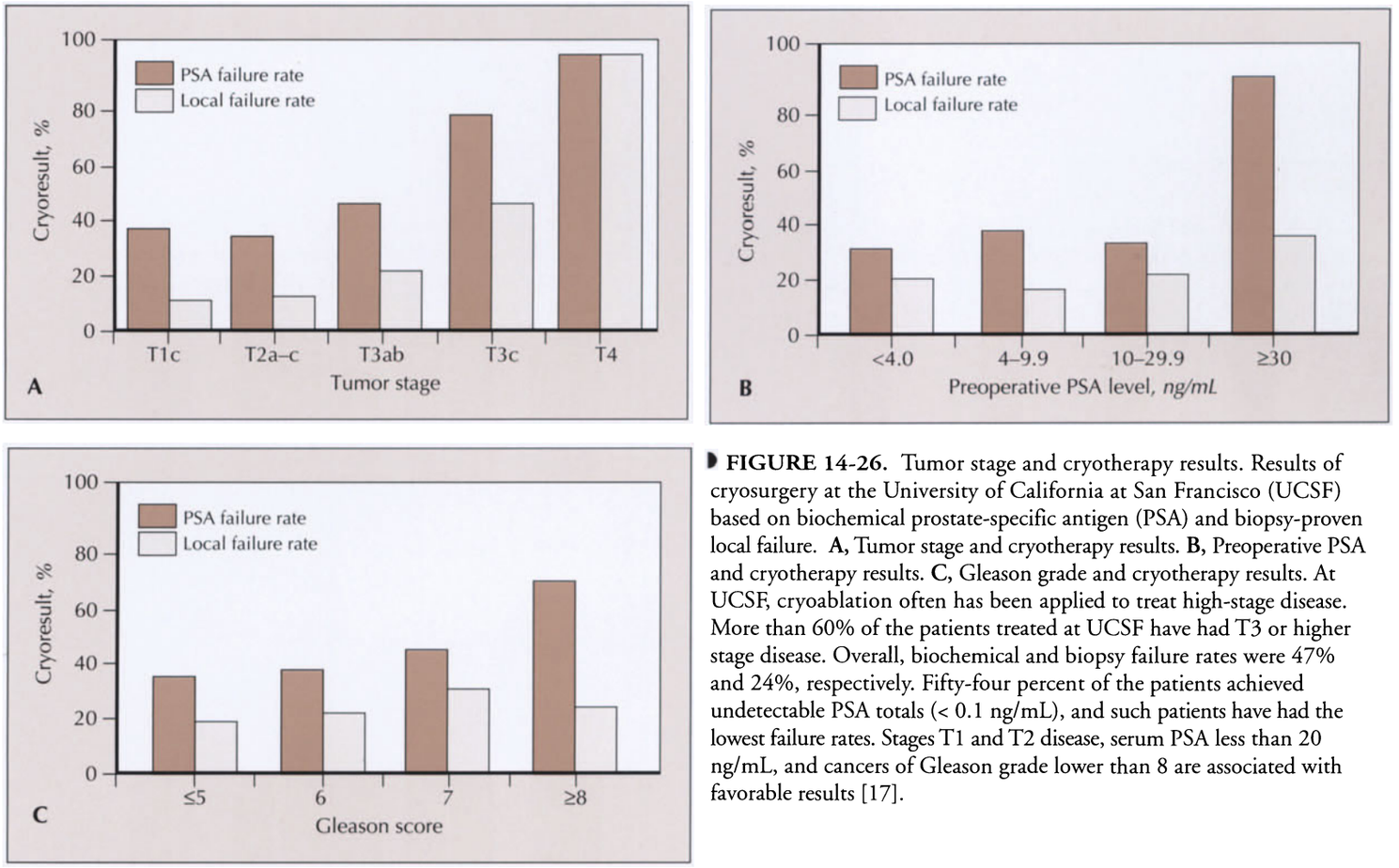

FIGURE 14-26. Tumor stage and cryotherapy results. Results of cryosurgery at the University of California at San Francisco (UCSF) based on biochemical prostate-specific antigen (PSA) and biopsy-proven local failure. **A,** Tumor stage and cryotherapy results. **B,** Preoperative PSA and cryotherapy results. **C,** Gleason grade and cryotherapy results. At UCSF, cryoablation often has been applied to treat high-stage disease. More than 60% of the patients treated at UCSF have had T3 or higher stage disease. Overall, biochemical and biopsy failure rates were 47% and 24%, respectively. Fifty-four percent of the patients achieved undetectable PSA totals (< 0.1 ng/mL), and such patients have had the lowest failure rates. Stages T1 and T2 disease, serum PSA less than 20 ng/mL, and cancers of Gleason grade lower than 8 are associated with favorable results [17].

Location of Residual Cancer After Cryoablation

	Preoperative Number of Cancers	Postoperative Number of Cancers	Residual Disease, %
Apex	42	4	9.5
Mid-prostate	49	2	4.1
Base	55	0	0.0
Seminal vesicle	16	7	43.8

FIGURE 14-27. Correlation between tumor location and local recurrence. Cancers at the apex or in the seminal vesicle are more likely to recur than are those confined to the midgland or base. Careful and complete cryoablation of tissue in cancers located at the apex and seminal vesicles is important. Preoperative careful mapping of the tumor location by multiple biopsies, including the biopsies of seminal vesicles, is essential for treatment planning.

Published Results of Cryosurgery

Study (Year)	Patients, n	Residual Cancer, %	Posttreatment PSA
Miller *et al.* [19] (1994)	62	21.0	0.59 ± 1.66 ng/mL (mean, 3 mo)
Coogan and McKiel [20] (1995)	87	17.0	≤ 0.2 ng/mL in 33.3% (1 y)
Bales *et al.* [21] (1995)	23	14.0	< 0.3 ng/mL in 14% (1 y)
Weider *et al.* [22] (1995)	61	13.1	< 0.5 ng/mL in 57.4% (3 mo)
Wake *et al.* [27] (1996)	63	25.0	< 0.1 ng/mL in 25% (3 mo)
Shinohara *et al.* [28] (1997)	102	23.0	< 0.1 ng/mL in 48% (3 mo)
Cohen *et al.* [29] (1996)	383	18.0	< 0.4 ng/mL in 55% (2 y)
Pisters *et al.* [24] (1997)	150	18.0	No increase > 0.2 ng/mL in 46%
Lee *et al.* [30] (1999)	81	2.5	0.12 and 0.07 ng/mL (mean and median)
de la Taille *et al.* [25] (2000)	43	Not reported	< 0.1 ng/mL in 60%
Long *et al.* [31] (2000)	975	18	< 0.5 in 60%, 45%, 36% for low-, intermediate-, high-risk group (5 y)
Chin *et al.* [32] (2001)*	118	6	< 0.5 ng/mL in 34% (50 mo)

*Radiation failure cases only.

FIGURE 14-28. Published results of cryoablation. The reported local failure rate after prostate cryoablation varies between 2.5% and 25%. Results correlate with stage and grade and the length of follow-up. Biochemical failure after cryoablation is not clearly defined, and the definition varies among series. The biochemical failure rate has been reported to range between 14% and 69%. Undetectable serum prostate-specific antigen (PSA) levels (*ie*, < 0.2 ng/mL) after cryosurgery are achieved in 33% to 58% of patients.

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Management of Metastatic Prostate Cancer

15

Maxwell V. Meng

The earlier diagnosis of prostate cancer has resulted in fewer men initially presenting with metastatic disease. In addition, the combination of more accurate pretreatment staging models with improved local treatment modalities has increased the number of men cured of prostate cancer. The management of metastatic prostate cancer relies on a variety of factors, including accurate diagnosis, formal staging, and appropriate treatment selection. Traditionally, metastatic disease was suspected because of symptoms and elevated serum phosphatase, and subsequently confirmed by a positive radionuclide bone scan. Newer concepts have emerged in defining prostate cancer metastases, including the use of prostate-specific antigen kinetics, imaging with a radiolabeled antibody to prostate-specific membrane antigen, and molecular detection of circulating prostate cancer cells.

Despite the numerous advances in all aspects of prostate cancer, treatment of metastatic prostate cancer remains fundamentally unchanged since the pioneering observations of Huggins and Hodges over 60 years ago [1]. The underlying basis was the recognition of androgen-dependent growth of prostate epithelial cells. Androgen deprivation was initially achieved by estrogen administration and then by surgical castration; today many more options are available to effect the endocrine treatment of prostate cancer. Controlled clinical trials in the 1960s helped to determine the appropriate doses of estrogens [2]. During the 1970s, the discovery of the hypothalamic control of pituitary secretion of luteinizing hormone led to the development of potent luteinizing hormone–releasing hormone (LHRH) agonists [3], enabling androgen deprivation without the need for surgical castration or the side effects of estrogen. The combination of testicular androgen suppression and adrenal androgen blockade (termed *maximal androgen blockade*, *total androgen blockade*, or *total androgen suppression*) was proposed as a novel regimen to improve outcomes in patients with metastatic disease [4]. However, benefits of combined androgen blockade, such as time to progression and overall survival, have not been demonstrated in numerous studies performed since the 1980s [5].

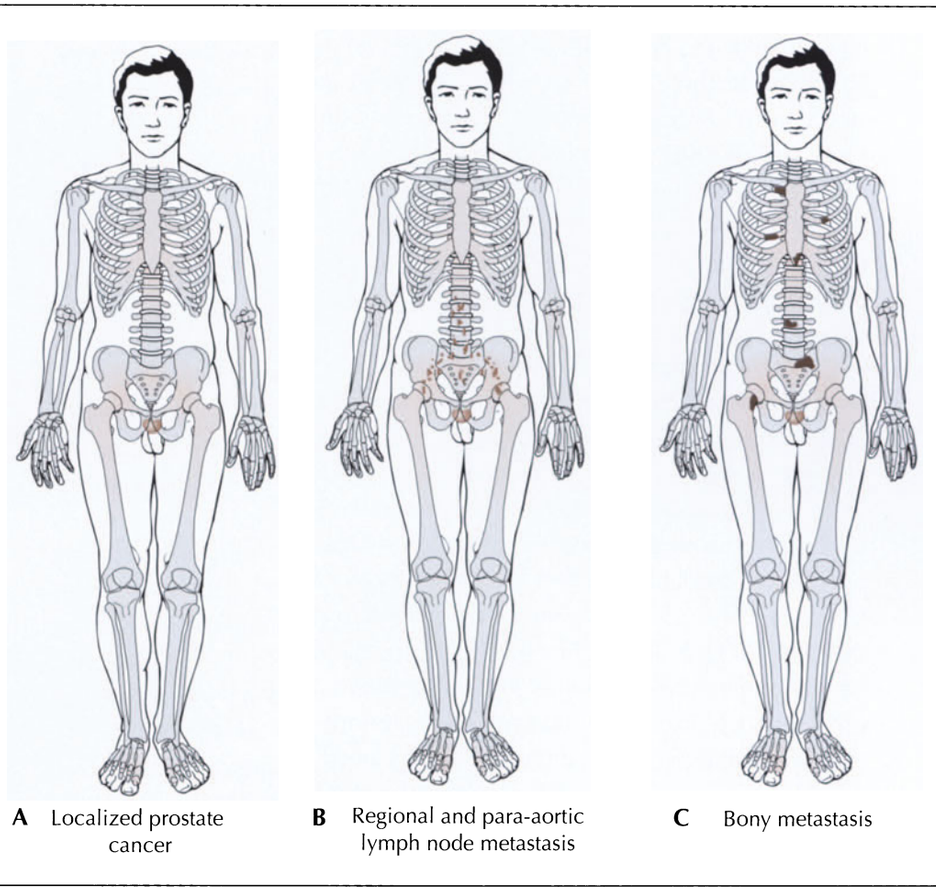
Newer approaches to hormonal therapy have focused on improving the quality of life and decreasing the side effects inherent with traditional hormonal manipulation. Potency-sparing therapies [6] and intermittent administration of LHRH agonists [7] are frequently performed with purported benefits, but adequate clinical trials have yet to prove the efficacy and advantages of these approaches compared with conventional regimens. More recently, the long-term economic costs, quality of life,

and morbidity have been discussed and should be included in the decision algorithms of patients undergoing androgen-deprivation therapy.

Ultimately, androgen deprivation is merely a palliative and not curative intervention for metastatic prostate cancer. Significant controversy surrounds the appropriate timing of treatment for those men with metastatic disease. Recent data suggest a survival benefit from early hormonal therapy [8,9]. However, eventually all men with metastatic prostate cancer progress and develop hormone-refractory prostate cancer. No peer-reviewed publication has shown that the treatment of hormone-refractory disease prolongs survival. Despite the obvious shortcomings of current therapies for hormone-refractory metastatic prostate cancer, advances in palliative management have been made, and a variety of experimental approaches are now being evaluated in clinical trials.

This chapter reviews the staging and management of metastatic prostate cancer. Both hormone-sensitive and hormone-refractory disease are discussed, with particular emphasis on state of the art concepts and management techniques.

IMAGING AND STAGING



A Localized prostate cancer

B Regional and para-aortic lymph node metastasis

C Bony metastasis

FIGURE 15-1. Typical regions of metastatic disease. **A,** Localized prostate cancer. **B,** Regional and para-aortic lymph node metastases. **C,** Bony metastases. Appropriate management of prostate cancer relies on the sensitive and specific detection of locoregional and distant metastatic disease. The most common sites of prostate cancer metastasis identified in pathologic studies are regional lymph nodes and bone; lung and liver metastases can also be found [10]. Identification of distant soft tissue metastases has traditionally relied on cross-sectional imaging with CT or MRI. Bone scans are the preferred method for detecting lesions in the bone. Contemporary imaging studies include radioimmunoscintigraphy and positron emission tomography. Prostate-specific antigen–producing cells can be detected with high sensitivity by the molecular technique of polymerase chain reaction. Definitive local therapy alone is doomed to failure, however, in those with underlying metastatic disease; thus, timely detection and some form of systemic therapy are required for optimal treatment in these patients.

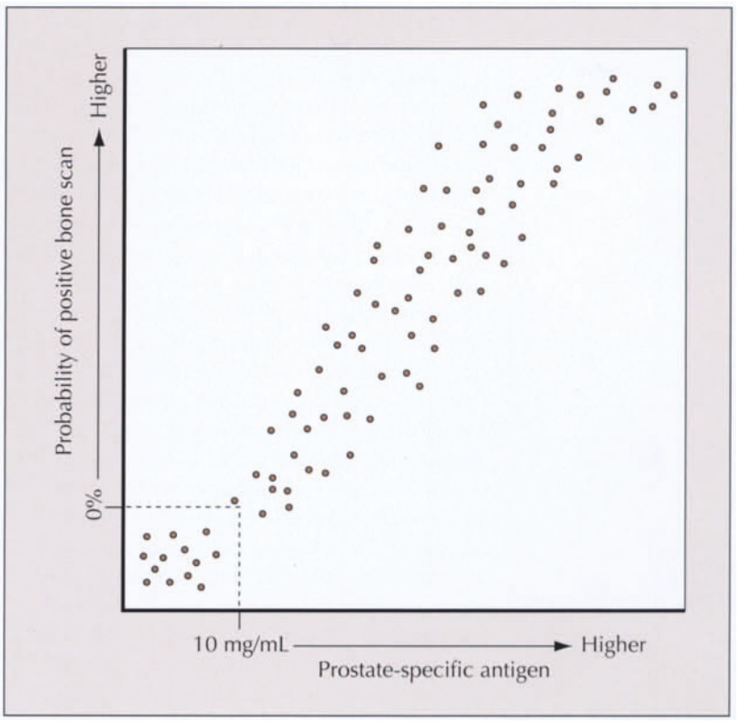


FIGURE 15-2. The probability of positive bone scans as predicted by serum prostate-specific antigen (PSA). Modern techniques of PSA determination and disease staging have greatly reduced the need for routine bone scans in patients diagnosed with clinically localized prostate cancer. If the serum PSA level is less than 10 ng/mL, the probability of detecting bony metastases by bone scan is low [11]. Furthermore, bone scans are not recommended in the post–radical prostatectomy patient with an undetectable PSA level [12] or PSA recurrence less than 30 to 40 ng/mL [13].

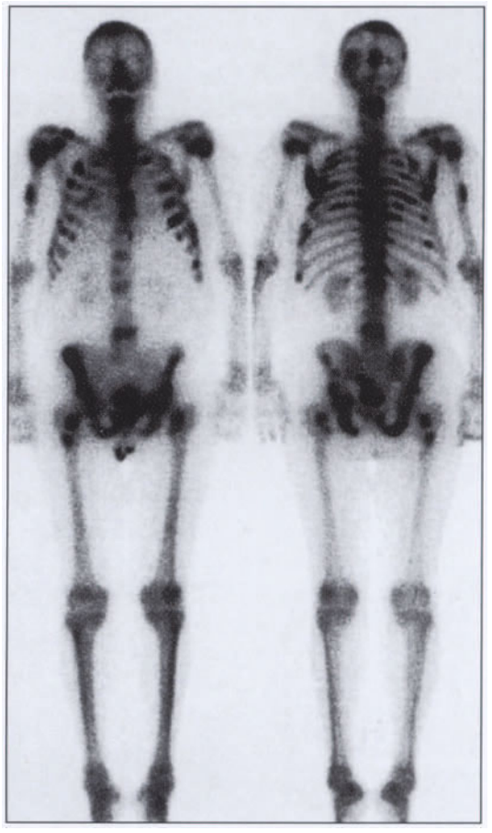
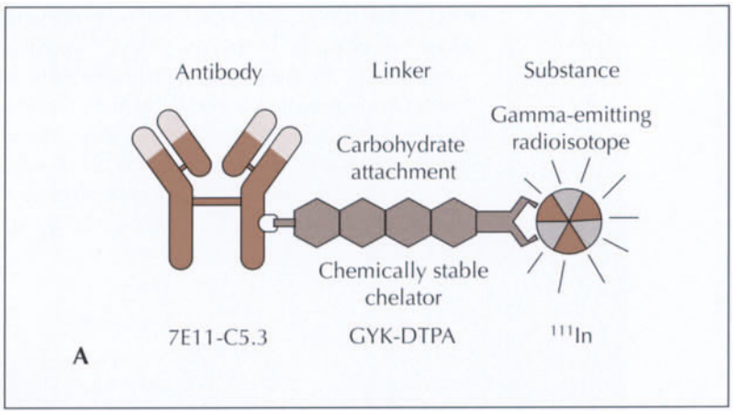
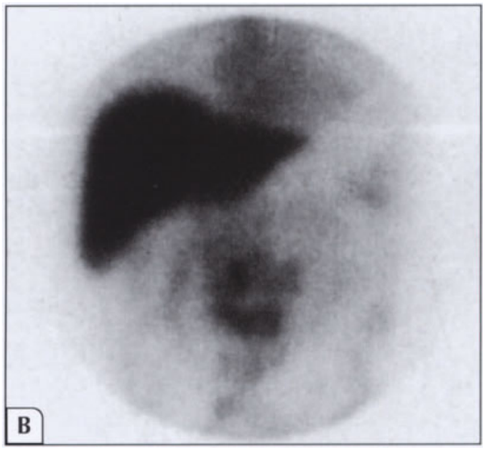


FIGURE 15-3. The radioscintigraphic bone scan is the most sensitive imaging method to detect metastases to bone. These lesions typically appear as asymmetric areas of increased tracer uptake, particularly in the axial skeleton. The advantages of bone scintigraphy include its high overall sensitivity, ability to evaluate the entire skeletal system, and relatively low cost. However, bone scans are limited because of the nonspecific information provided. Areas of increased radiotracer uptake can be associated with a number of nonmalignant etiologies, such as trauma, arthritis, and Paget's disease. (*From* Manyak [14]; with permission.)





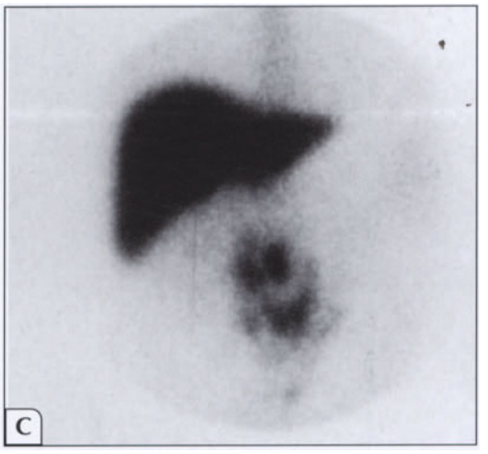


FIGURE 15-4. Application of a radiolabeled monoclonal antibody for detection of prostate cancer. **A,** Product formulation of this radiolabeled monoclonal antibody (ProstaScint; Cytogen, Princeton, NJ). **B** and **C,** Images of metastatic disease obtained using capromab pendetide radioimmunoscintigraphy. Although CT and MRI are well-accepted for staging many malignancies, studies in prostate cancer indicate that these modalities have poor sensitivity in detecting early metastases. In 1996, the Food and Drug Administration approved the use of a radiolabeled monoclonal antibody to prostate-specific membrane antigen in patients with 1) newly diagnosed prostate cancer at high risk for lymph node metastases, and 2) a rising prostate-specific antigen and no demonstrable site of recurrence after prostatectomy. This radiolabeled antibody (^{111}In-labeled capromab pendetide) is able to image prostate cancer soft tissue metastases with greater sensitivity than traditional radiographic tests [15,16]. Unfortunately, the test is cumbersome to administer, requiring a period of 3 to 4 days, and both false-negative and false-positive results are obtained in up to 30% of cases. Newer imaging agents, such as ^{18}F-fluorodeoxyglucose and ^{11}C-methionine, take advantage of differences in the metabolic activity between benign and malignant tissues [17]. However, the clinical role of positron emission tomography in prostate cancer requires further investigation (*Panels B and C from* Manyak [14]; with permission.)

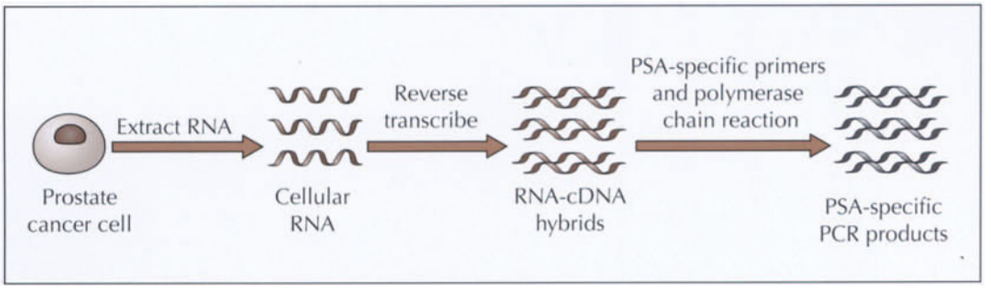


FIGURE 15-5. Detection of prostate-specific antigen (PSA)–producing cells by reverse transcription polymerase chain reaction (RT-PCR). This method can potentially detect one PSA-producing cell in a background of 10,000,000 non-PSA–producing cells. RT-PCR has been used to detect PSA-producing cells from several sources, including blood, bone marrow, and lymph nodes [18–20]. Messenger RNA is purified from a cellular source and reverse transcribed, and then PSA-specific message is amplified using specific primers and the polymerase chain reaction. Debate surrounds this extremely sensitive method of molecular staging, with the uncertain relevance of detecting PSA-specific messenger RNA in the blood stream [20]. The clinical validity of observations related to RT-PCR must be confirmed in multicenter trials. A variety of other potential prostate-specific messenger RNAs (*eg*, prostate-specific membrane antigen) can also be assayed by RT-PCR.

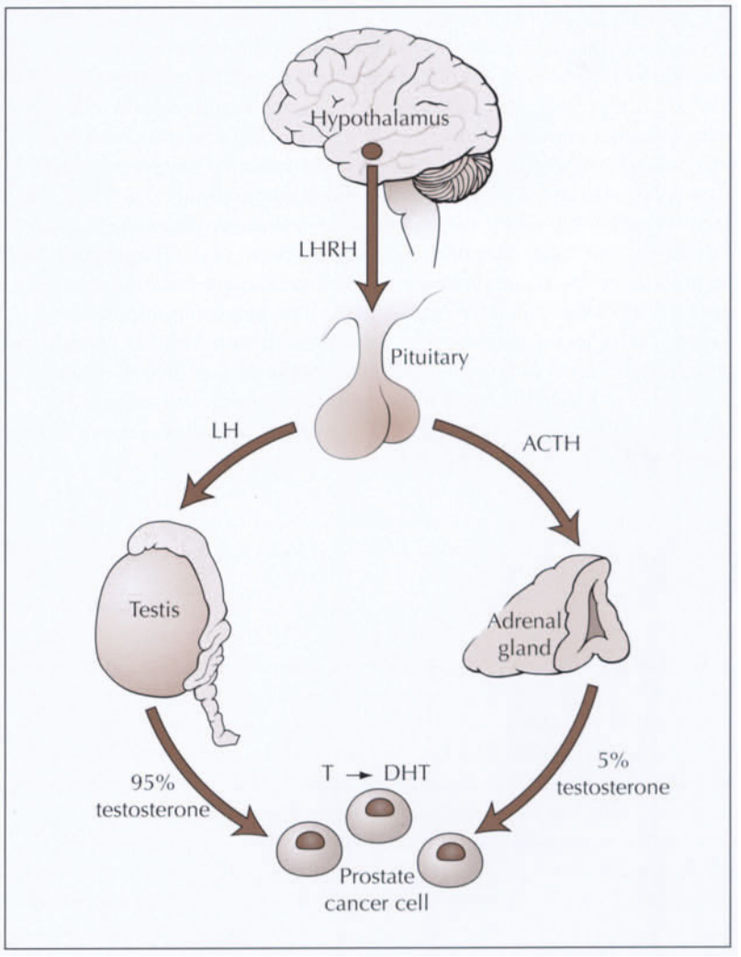


FIGURE 15-6. Sources of androgen production and control of androgen secretion. Luteinizing hormone–releasing hormone (LHRH) is secreted into the hypophyseal portal system in pulses and circulates to the pituitary, where it stimulates the release of luteinizing hormone (LH) from gonadotrophs. LH binds to specific receptors in testicular Leydig cells, resulting in the production and secretion of testosterone into the bloodstream. This pathway accounts for approximately 95% of circulating testosterone. The remaining 5% is derived from the adrenal cortex, under the control of pituitary adrenocorticotropic hormone (ACTH). DHT—dihydrotestosterone; T—testosterone.

ENDOCRINE FACTORS

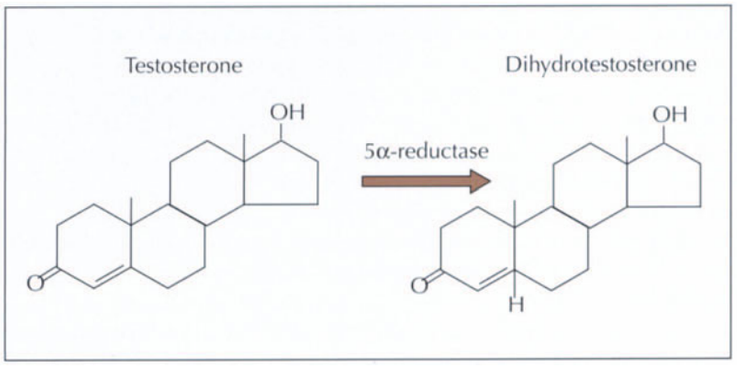


FIGURE 15-7. Conversion of testosterone to dihydrotestosterone is catalyzed by 5α-reductase enzymes. Although testosterone is the primary plasma androgen secreted by the testes, testosterone is converted to dihydrotestosterone, a more potent androgen, by the enzyme 5α-reductase. The two isoforms of 5α-reductase, type I and II, are specifically found in the skin/liver, and prostate, respectively. Selective inhibition of type II 5α-reductase activity by the 4-azasteroid finasteride (Proscar; Merck & Co., Inc., Whitehouse Station, NJ) decreases serum prostate-specific antigen (PSA) and reduces prostate gland size. Inhibitors of 5α-reductase, both alone and in conjunction with other agents, are being evaluated as anticancer therapy.

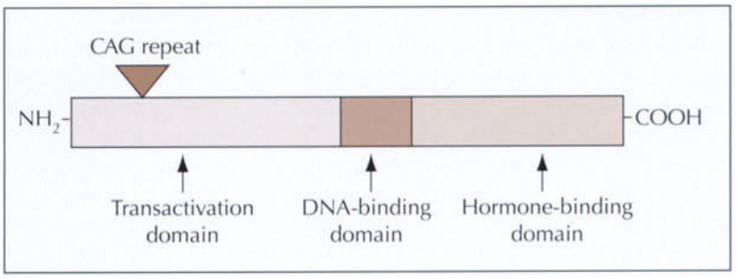


FIGURE 15-8. Androgenic actions are mediated by a ligand-dependent transcriptional regulator: the androgen receptor. The androgen receptor is a member of the nuclear steroid receptor superfamily that includes the progesterone, estrogen, and glucocorticoid receptors [21]. Three distinct domains characterize the 917-amino acid protein: 1) a central DNA-binding domain flanked by 2) an amino-terminal transactivation domain, and 3) a carboxy-terminal hormone-binding domain. The transactivation domain contains a variable number of glutamine (CAG) repeats that modulate function. Androgen binding to the receptor results in protein conformational change, homodimerization, and binding to specific hormone-response elements with subsequent transcriptional regulation [22]. These changes in gene expression, in turn, regulate growth and differentiation in a variety of androgen-sensitive tissues, including the prostate. The recent discovery of coregulatory proteins has suggested mechanisms for the development of androgen-independent growth and novel targets of therapy [23].

HORMONAL THERAPY

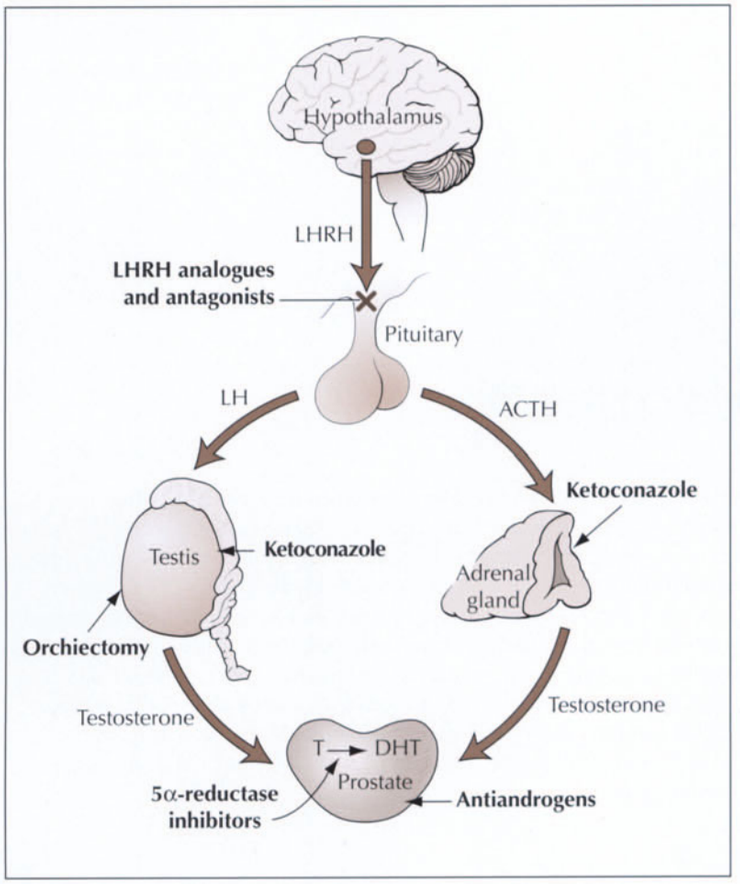


FIGURE 15-9. Blockade of androgen action. Blockade of androgen action can be achieved via many routes. Elucidating the hormonal control mechanisms underlying prostate growth has given physicians multiple potential targets for therapeutic intervention. The gold standard for eliminating gonadal androgen secretion remains bilateral orchiectomy, a procedure reported over 50 years ago for the treatment of prostate cancer [1]. Within hours of surgical castration, 95% reduction in serum testosterone levels is achieved. The luteinizing hormone–releasing hormone (LHRH) analogues currently approved by the US Food and Drug Administration potently bind and stimulate the pituitary LHRH receptors. This sustained agonist activity initially results in a marked increase in luteinizing hormone (LH) and testosterone (T) secretion, but is followed by a paradoxic decline to castrate testosterone levels after 2 to 4 weeks. Current LHRH agonists, such as leuprolide and goserelin acetate, are available in depot formulations capable of suppressing testosterone secretion for 3, 4, or 12 months per subcutaneous injection [24]. Estrogens such as diethylstilbestrol (DES) have been used in the treatment of prostate cancer for decades. DES, no longer manufactured in the United States, acts as a potent inhibitor of LH secretion [25], thereby indirectly lowering testosterone secretion. Antiandrogens block the effects of androgens by competitively binding the androgen receptor. Both steroidal (cyproterone acetate) and nonsteroidal (flutamide, bicalutamide, and nilutamide) antiandrogens have been used in the treatment of prostate cancer. These agents inhibit the effects of androgens on the pituitary as well as prostatic tissue; however, only pure (nonsteroidal) antiandrogen monotherapy is associated with a temporary rise in plasma testosterone [26]. A variety of agents can inhibit adrenal androgen secretion. Those most commonly used in prostate cancer are ketoconazole and aminoglutethimide, which interfere with cytochrome P-450 hydroxylation reactions. Ketoconazole also inhibits testicular androgen production and can be used to rapidly achieve castrate levels of testosterone within 24 to 48 hours [27]. ATCH—corticotropin; DHT—dihydrotestosterone.

Toxicities of Hormonal Therapies

	Decreased Libido	Decreased Potency	Gynecomastia	Edema	Hot Flashes	Fatigue
Orchiectomy	++++	++++	++	+	++++	++
LHRH	++++	++++	++	+	++++	++
Estrogens	++++	++++	++++	+++	+	++
Anti-androgens	++	++	+++	+	++	++

Plus signs *indicate degree of toxicity.*

FIGURE 15-10. Toxicities of hormonal therapies. Although hormonal therapies are well tolerated when compared with most other cancer treatments, significant side effects are associated with traditional hormonal manipulation. The loss of sexual function, both libido and potency, is particularly distressing to many patients. Some men have considerable psychologic difficulty undergoing orchiectomy, and most choose alternative therapies if given a choice. Long-term effects of hormonal therapy can include hot flashes, loss of muscle mass, fatigue, anemia, osteoporosis, and depression [28]. Additional problems of thromboembolic events, fluid retention, and cardiovascular mortality can be encountered when estrogens are used. Antiandrogen monotherapy, or in combination with a 5α-reductase inhibitor, is associated with a lower incidence of sexual dysfunction than traditional hormonal therapy. LHRH—luteinizing hormone–releasing hormone.

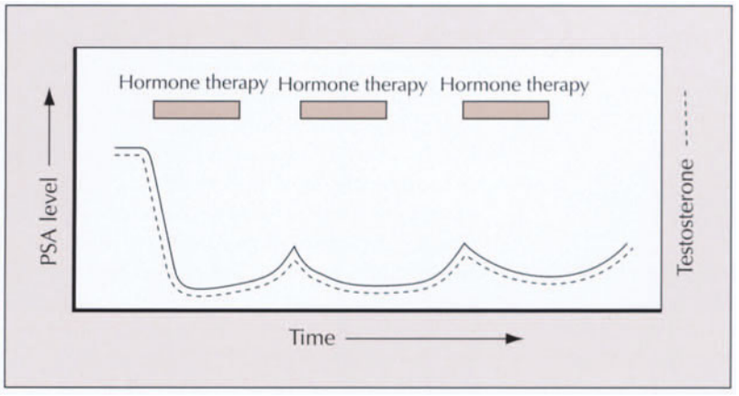


FIGURE 15-11. Intermittent androgen deprivation. The concept of intermittent rather than continuous androgen suppression has recently been proposed. In animal studies, data suggest that intermittent therapy may delay the onset of hormone-refractory prostate cancer [29]. In addition, men often prefer to have periods off hormonal therapy when their sexual function may return to normal. Although many variations of intermittent therapy have been reported, most closely monitor serum prostate-specific antigen (PSA) level and utilize PSA changes to dictate subsequent treatment decisions [30]. No randomized studies comparing intermittent with continuous hormonal therapies have been published, so definitive conclusions cannot yet be drawn.

Experimental Forms of Hormone Therapy

LHRH antagonists
Abarelix (PPI-149)
Antarelix
Cetrorelix (SB-75)
Ganirelix
Iturelix
Dual 5α-reductase inhibitors
LY320236
FK143
FCE 28260
GG745
Miscellaneous
PC-SPES

FIGURE 15-12. Experimental hormonal therapy. Orchiectomy, estrogens, and luteinizing hormone–releasing hormone (LHRH) agonists are well described in the prostate cancer literature. Newer forms of hormonal therapy are being developed. These experimental forms of hormonal therapy include novel 5α-reductase inhibitors and LHRH antagonists. 5α-Reductase inhibitors block conversion of testosterone to the more potent dihydrotesterone. Two isoforms of the 5α-reductase enzyme (type I and II) are expressed in a tissue-specific manner. Although type II inhibitors such as finasteride are clearly inadequate to treat prostate cancer, compounds that inhibit both types I and II enzymes are under active investigation [31]. Recent phase III studies of the LHRH antagonist abarelix has demonstrated clinical efficacy in patients with prostate cancer [32]. The advantages of LHRH antagonists primarily relate to the lack of initial luteinizing hormone flare expected with LHRH analogues. Furthermore, use of LHRH antagonists avoids the effects of small increases in testosterone associated with each LHRH agonist injection and also causes long-term suppression of follicle-stimulating hormone, a potential growth factor for prostate cancer. It is possible that LHRH antagonists will replace current agonists for the treatment of prostate cancer.

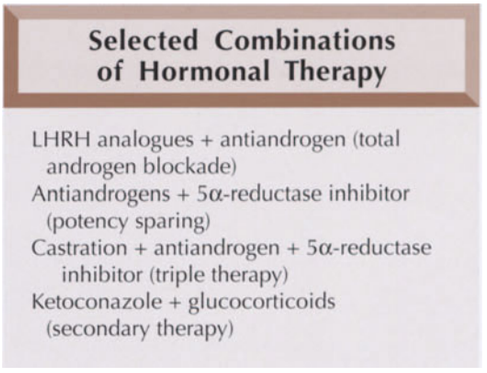


FIGURE 15-13. Selected combinations of hormonal therapy. Combinations of hormonal therapy have been carefully evaluated over the past several decades. Complete androgen blockade achieved by testicular castration and an antiandrogen has certain theoretical advantages over luteinizing hormone–releasing hormone (LHRH) agonist monotherapy. Although some prospective randomized trials have reported a survival benefit while using combinations of LHRH analogues and antiandrogens [33], meta-analysis of all trials demonstrate that the effects are relatively minor [5]. Orchiectomy and antiandrogens have also been evaluated in prospective trials, but recent results do not indicate an advantage of this combined approach [34]. Antiandrogens, such as flutamide, have been used with the 5α-reductase inhibitor finasteride in an effort to diminish the side effects of traditional hormonal therapy [35]. This combination is associated with less sexual dysfunction than LHRH analogues or orchiectomy. However, equivalent clinical efficacy has not been shown in controlled trials.

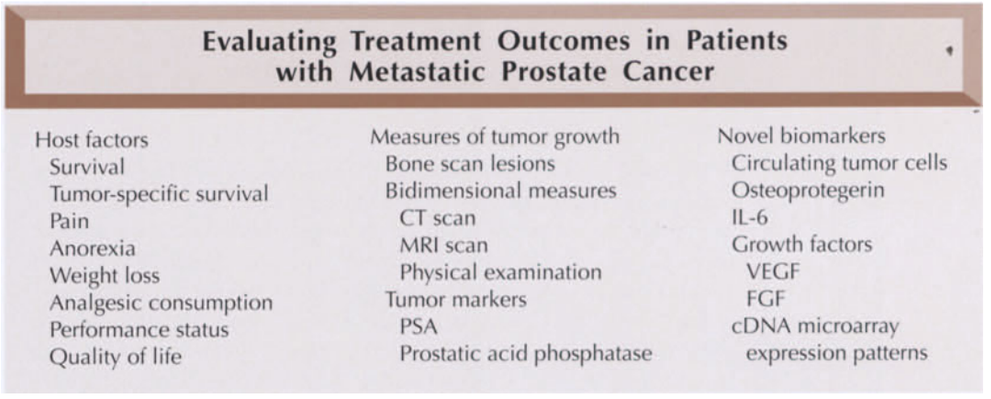


FIGURE 15-14. Evaluating treatment outcomes in patients with metastatic prostate cancer. The efficacy of any treatment must be measured by standardized and generally recognized endpoints. Commonly evaluated endpoints include both host- and tumor-specific effects as well as treatment-associated toxicities. In patients with advanced prostate cancer, host-oriented endpoints include overall survival, tumor-specific survival, pain, anorexia, weight loss, analgesic consumption, performance status, and quality of life. Some of these have been formally defined by various validated tools. Tumor-specific endpoints include radiographic changes, physical findings, and biopsy findings, as well as a variety of markers which either directly (*eg*, prostate-specific antigen [PSA] and prostatic acid phosphatase) or indirectly (*eg*, alkaline phosphatase and hemoglobin) reflect tumor activity. Each of these endpoints can be evaluated statistically in terms of absolute change, duration of change, or duration without progression (progression-free survival). Most physicians view host-specific factors as most helpful in evaluating the efficacy of therapies. The discovery of novel biomarkers, both molecular and biochemical, may enable improved selection of patients likely to respond as well as accurate assessment of response to therapy and disease status. Current candidates include angiogenic growth factors, osteoprotegerin, interleukin-6 (IL-6), and gene expression profiles on cDNA microarray [36]. FGF—fibroblast growth factor; VEGF—vascular endothelial growth factor.

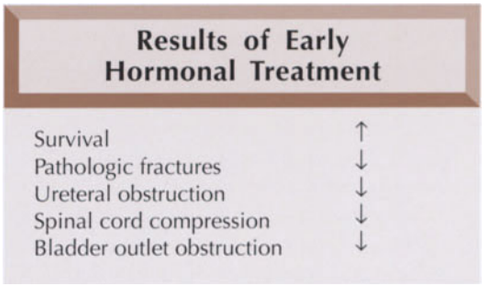


FIGURE 15-15. Early hormonal treatment has improved survival and decreased morbidity in controlled randomized trials [8,9]. Despite the consensus that androgen deprivation is currently the best available treatment for patients with metastatic prostate cancer, significant controversy remains as to when these therapies should be initiated. As with many areas of prostate cancer, uncertainty exists because of a paucity of prospective trials comparing the various treatments. Data from the UK's Medical Research Council group [8] provide some insight into the effects of immediate versus deferred treatment for advanced prostate cancer. In this study, patients were randomly assigned to receive treatment either immediately at the time that the disease was diagnosed, or at the time of "clinically significant progression." This study indicated a survival advantage for patients treated with immediate hormonal therapy; subset analysis revealed that this advantage was confined to those patients with nonmetastatic (TxNxM0) disease. These results suggest that once a patient is diagnosed with stage M1 disease, it is too late for immediate therapy to confer a survival advantage. Potential advantages of immediate hormonal therapy were not limited to survival. Pathologic fracture, ureteral obstruction, spinal cord compression, and surgical intervention for bladder outlet obstruction were significantly increased in those patients receiving delayed therapy. The Eastern Cooperative Oncology group compared immediate hormonal therapy with observation in men with positive lymph nodes undergoing prostatectomy [9]. At median follow-up of 7 years, patients receiving immediate therapy had a statistically significant survival advantage. Results of the similar European Organization for Research and Treatment of Cancer 30846 trial are anxiously awaited to help shed light on the timely issue of immediate versus delayed androgen deprivation [37].

Criteria for Diagnosis of Hormone-refractory Prostate Cancer

Castrate levels of testosterone
Progressive disease
- PSA level
- Bone scan
- Soft tissue disease
- Symptoms

FIGURE 15-16. Criteria for the diagnosis of hormone-refractory prostate cancer. The definition of hormone-refractory disease has changed dramatically as our ability to monitor the effects of therapy and the progression of prostate cancer has become more precise. Before the era of radioimmunoassay, definitions of hormone-refractory disease did not include the measurement of testosterone levels. Today, many physicians believe that testosterone must be suppressed below castrate levels (0.2 ng/mL) before patients can be truly labeled as "hormone refractory." More importantly, application of different criteria can significantly change the population of patients in question. Traditional criteria relied on the onset of new symptoms or new lesions on radiologic imaging tests. Currently, increases in prostate-specific antigen (PSA) levels have become accepted as evaluable and appropriate surrogate endpoints. However, the precise definition of an "increasing" PSA is subject to controversy [38]. Some investigators suggest that any confirmed rise in PSA constitutes disease progression, whereas others have used minimal PSA values (< 10 ng/mL) or percentage increases over PSA nadir (*eg*, 50% increase over nadir values) as definitions of hormone-refractory disease.

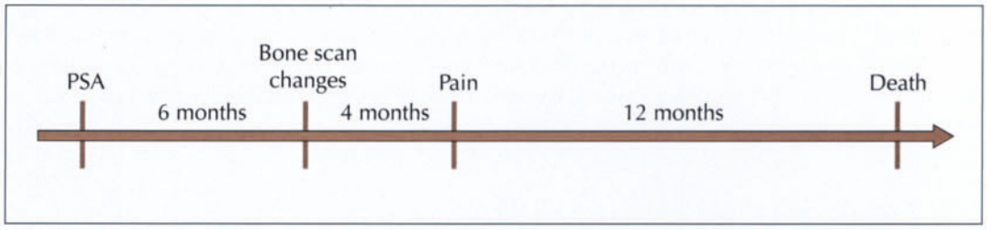


FIGURE 15-17. Natural history of hormone-refractory prostate cancer. As the natural history of hormone-refractory prostate cancer is better understood, it is generally agreed that prostate-specific antigen (PSA) elevations precede progression on bone scans, and that progression on bone scans typically precedes changes in clinical symptoms. Studies of patients with stage D2 disease indicate that PSA rises occur 6 months before bone scan changes, and that bone scan changes will precede pain by approximately 4 months [39]. For patients with pain, the average life expectancy is less than 1 year. When evaluating the literature regarding hormone-refractory prostate cancer, it is essential to carefully ascertain the definition of hormone-refractory disease used in each particular study in order to assess the reported therapeutic results.

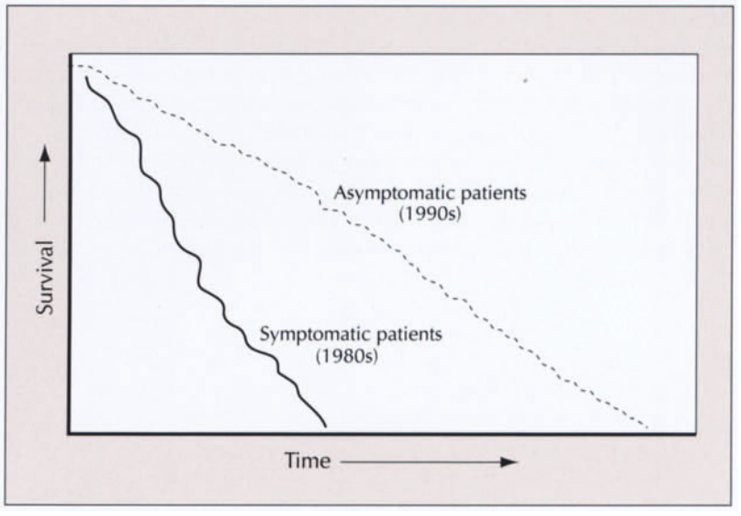


FIGURE 15-18. Survival with hormone-refractory prostate cancer. Survival of patients with hormone-refractory prostate cancer has become progressively longer, but no peer-reviewed study or prospective randomized trial has yet shown a survival advantage of one treatment over another. The survival of patients in various trials has depended primarily on the type of patients enrolled in that trial rather than the therapy used. Recent studies have shown longer survival compared with older trials, but this may be due to lead-time bias from the use of prostate-specific antigen values, rather than symptoms, when enrolling patients in hormone-refractory protocols.

Treatment Options for Hormone-refractory Prostate Cancer

- Withdrawal therapies
- Secondary hormonal therapies
- Radiation therapies
- Chemotherapy
- Experimental therapies
  - Antiangiogenesis
  - Suramin
  - Gene therapy
  - Immunotherapy

FIGURE 15-19. Treatment options for hormone-refractory prostate cancer. The treatment options for hormone-refractory prostate cancer can be divided into withdrawal therapies, secondary hormonal therapies, irradiation, chemotherapy, and experimental approaches. Withdrawal therapies have been described in recent years and can influence both patient care and clinical trial results.

Some patients in whom initial hormonal therapy with standard approaches fails (*eg*, luteinizing hormone–releasing hormone analogues, orchiectomy) can have subjective and objective responses to secondary hormonal manipulation. Radiation therapy for advanced prostate cancer can be delivered by either external beam or intravenous methods.

Withdrawal Responses in Hormone-refractory Prostate Cancer

- Antiandrogens
  - Flutamide
  - Bicalutamide
  - Nilutamide
- Estrogens
- Megestrol acetate
- Estramustine
- Retinoids
- TNP-470

FIGURE 15-20. Withdrawal responses in hormone-refractory prostate cancer. Some patients may benefit from withdrawal of the therapeutic agent as well as its administration. Withdrawal responses were initially recognized with the antiandrogen flutamide [40,41] but now include bicalutamide, nilutamide, estrogens [42], megestrol acetate [43], estramustine [44], and the antiangiogenic agent TNP-470 [45]. Currently, all agents (except one) having withdrawal activity in prostate cancer are known to interact with steroid receptors. The mechanism of withdrawal activities is unclear, but a commonly cited hypothesis involves the development of mutant receptors that recognize antiandrogens as receptor agonists rather than antagonists. Thus, secondary withdrawal of the agent decreases receptor activation and growth stimulation.

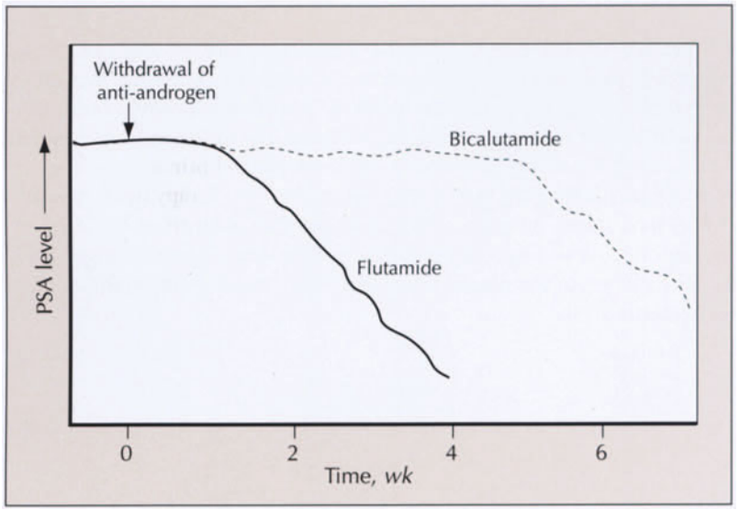


FIGURE 15-21. Kinetics of withdrawal responses. Withdrawal responses vary by agent. Although withdrawal activity has now been described for all antiandrogens, clinically significant differences have been noted among these compounds [46]. For instance, responses to flutamide discontinuation are typically noted within 2 weeks, whereas bicalutamide withdrawal responses are delayed 6 to 8 weeks after the agent is discontinued. Differences in the kinetics of the withdrawal responses may be related to the various functional half-lives of the agents; flutamide has a serum half-life of approximately 6 hours whereas bicalutamide has a half-life of approximately 6 days. PSA—prostate-specific antigen.

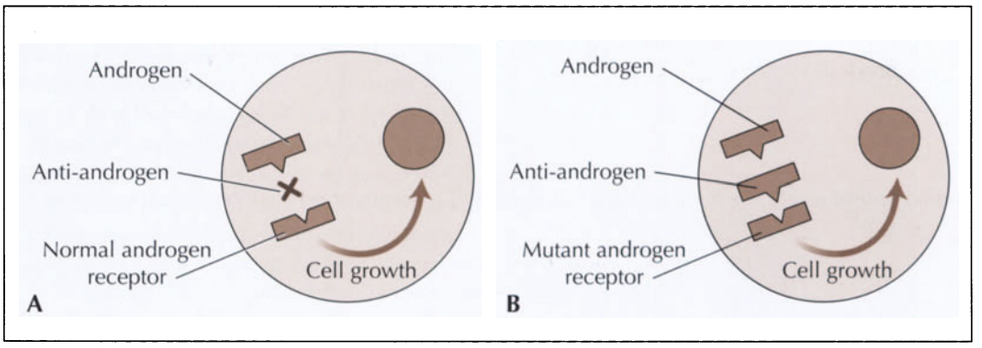


FIGURE 15-22. Normal versus mutant androgen receptor activity. **A,** Normal androgen receptor actions are blocked by antiandrogens. **B,** Mutant androgen receptor can be activated by antiandrogens. Although the clinical significance of mutant androgen receptors is debated, most investigators agree that mutations can be detected in selected patients with prostate cancer [47]. Most of the controversy relates to the frequency, location, and role of these mutations. Because the androgen receptor gene is X-linked, there is only one allele per cell. Thus, any genetic change in these sequences would not be complemented by the action of a normal gene expressed on another chromosome. The potential importance of mutations is therefore magnified when compared with biallelic genes. The first androgen receptor mutation described in patient-derived material was sequenced from the LNCaP cell line. The LNCaP androgen receptor possesses a point mutation within the hormone-binding domain [48], resulting in the functional ability to recognize a variety of ligands in a promiscuous manner. Instead of specific receptor activation by androgens and blockage by antiandrogens, mutant receptor activation could be triggered by a variety of membrane-soluble compounds including antiandrogens, estrogens, and progesterone. In patients with hormone-refractory prostate cancer, clinical antitumor responses after antiandrogen withdrawal may be linked to the presence of such mutations in the hormone-binding domain of the androgen receptors expressed at sufficient levels.

Hormonal Treatments for Hormone-refractory Prostate Cancer

- Antiandrogens
  - Flutamide
  - Bicalutamide
  - Nilutamide
- Glucocorticoids
  - Prednisone
  - Dexamethasone
  - Hydrocortisone
- Estrogens
  - Diethylstilbestrol
  - DES diphosphate
- PC-SPES
  - Estramustine (other activities reported)
- Progesterones
  - Megestrol acetate
- Adrenal suppressives
  - Ketoconazole
  - Aminoglutethimide

FIGURE 15-23. Secondary hormonal treatments for hormone-refractory prostate cancer. Antiandrogens [49], glucocorticoids [50], adrenal suppressive agents such as ketoconazole [51], megestrol acetate [52], estrogens [53], and estramustine [54] are all known to interact with hormonal receptors and have some activity in patients with hormone-refractory prostate cancer. The duration of responses typically is limited to 2 to 4 months. The described activity of these *hormonal* agents in patients with cancer progression despite androgen deprivation underscores the ambiguity of the current nomenclature; a more accurate sequence may be as follows: hormone-sensitive to hormone-responsive to truly hormone-refractory disease.

Radioisotopes in Treatment of Hormone-refractory Prostate Cancer

Product	*Half-life, d*	*Decay*	*Energy (β-MeV) max*
^{89}Sr	50.5	β^-	1.46
^{153}Sm	1.9	β^-, γ	0.81
^{32}P	13.6	β^-	1.71
^{186}Re	3.8	β^-, γ	1.07
^{188}Re	0.7	β^-	2.12

FIGURE 15-24. Radioisotopes in the treatment of hormone-refractory prostate cancer. Radiation therapy has long been known to provide effective palliation for patients with advanced prostate cancer. Although external beam radiation has been the most popular modality, newer data suggest that radioisotopes administered intravenously also have significant therapeutic effects, particularly in patients with painful bony metastasis. Radioactive phosphorus (^{32}P) has long been available, but in recent years several other therapeutic bone-seeking radioisotopes have been introduced, including ^{89}Sr and ^{153}Sm. A comparison of these isotopes demonstrates significant differences in physical half-life and particle energy.

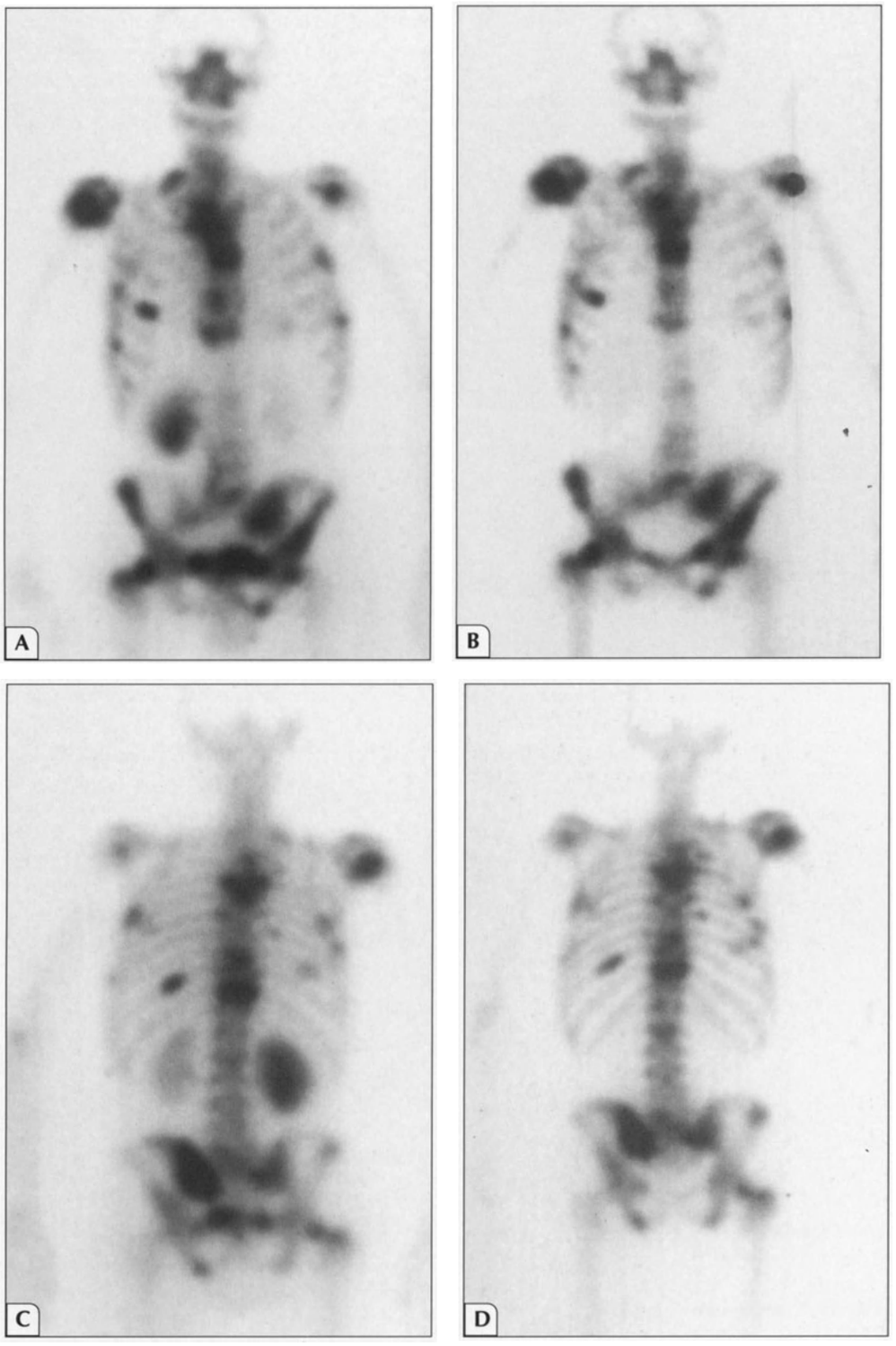


FIGURE 15-25. The use of ^{153}Sm-EDTMP in imaging and treatment. Because ^{153}Sm is a β- and γ-emitting isotope, simultaneous imaging and treatment can be accomplished with a single agent. No difference in imaging can be readily distinguished between conventional bone scans (**A** and **C**) and ^{153}Sm-EDTMP (**B** and **D**). Identifying the crucial role of the bone microenvironment in prostate cancer may have implications for understanding the pathogenesis of disease progression [55,56] and clinical therapy with bisphosphonates [57].

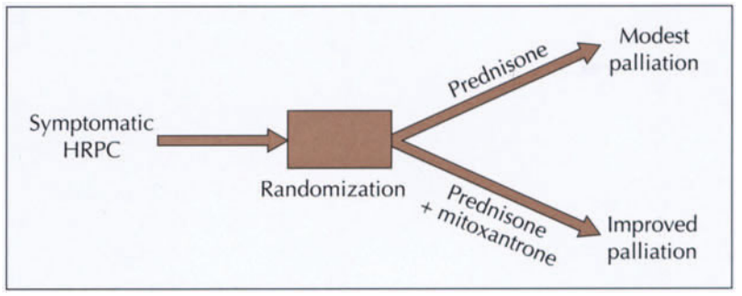


FIGURE 15-26. Mitoxantrone in the treatment of hormone-refractory prostate cancer. Although chemotherapy has not been traditionally perceived as efficacious in patients with prostate cancer, recent data from prospective randomized trials indicate that mitoxantrone plus low-dose prednisone is superior to low-dose prednisone alone in achieving pain relief in patients with symptomatic, metastatic hormone-refractory prostate cancer. Tannock *et al.* [50] demonstrated that the percentage of patients achieving pain relief or having declines in analgesic consumption was substantially higher in those receiving mitoxantrone. The combination with an antisense oligonucleotide complementary to *Bcl*-2 messenger RNA is well-tolerated [58] and may form the basis of other novel mitoxantrone-based regimens. HRPC—hormone-refractory prostate cancer.

Estramustine-based Chemotherapy

Combination	*PSA Decline > 50%*
Estramustine + vinblastine	61%
Estramustine + VP-16	58%
Estramustine + paclitaxel	53%
Estramustine + docetaxel	63%
Estramustine + vinorelbine	24%
Estramustine + docetaxel + trastuzumab	69%

FIGURE 15-27. Estramustine-based chemotherapy. Estramustine-based chemotherapies have been evaluated in phase I and II trials in patients with advanced prostate cancer. Estramustine, an agent with both hormonal and cytotoxic properties, has been combined with a variety of chemotherapeutic agents that inhibit microtubule formation. In vitro studies indicate a possible synergism with these combinations. Promising results from phase I and II clinical trials have been reported with estramustine and vinblastine [59], estramustine and VP-16 [60], estramustine and paclitaxel [61], estramustine and docetaxel [62], estramustine and vinorelbine [63], and estramustine and docetaxel and trastuzumab (monoclonal antibody to HER2 receptor) [64].

Endogenous Angiogenic Stimulators and Inhibitors

Endogenous angiogenic stimulators
- Interleukin-8
- NF-κB
- Fibroblast growth factors
- Angiogenin
- Transforming growth factors (α and β)
- Platelet-derived growth factor
- Angiotropin
- Vascular-endothelial growth factor

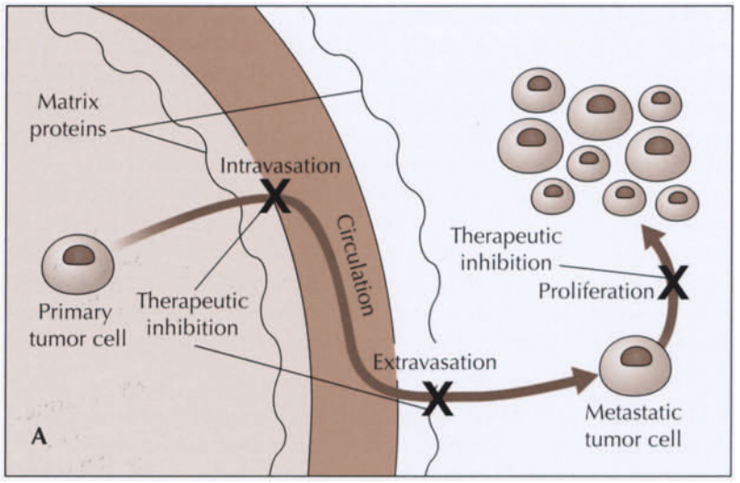
Endogenous angiogenic inhibitors
- Angiostatin
- Endostatin
- Platelet factor-4
- Glucocorticoids
- Interferons (α and β)
- Thrombospondin-1

FIGURE 15-28. Endogenous angiogenic and antiangiogenic factors regulate new blood vessel formation. Angiogenesis is essential for tumor expansion and metastasis. Tumor cells can stimulate the proliferation of endothelial cells and new capillaries, providing additional nutrients for tumor growth and avenues for spread. This angiogenic response appears to be a result of changes in the tightly controlled balance between endogenous inhibitors and inducers [65]. Inhibition of this phenomenon is a potential therapeutic modality that has been the focus of much research.

Inhibitors of Angiogenesis

- TNP-470
- Carboxyamidotriazole
- Thalidomide
- Pentosan polysulfate
- Interferon-α
- Vitamin D_3 analogues
- Endostatin
- Angiostatin
- SU101 (platelet-derived growth factor receptor inhibitor)

FIGURE 15-29. Inhibitors of angiogenesis currently in various phases of drug development. A variety of antiangiogenic factors are being evaluated in clinical trials [66,67]. Endogenous inhibitors have received considerable attention because of effectiveness in animal models. Endostatin is a 20-kD C-terminal fragment of collagen XVIII. Angiostatin is a 38-kD fragment of plasminogen.



B. Antimetastatic Agents

Batimistat	AG3340
Marimistat	CGS-27023A
Ilomastat	COL-3

FIGURE 15-30. Metastasis and antimetastatic agents. **A,** The complexity of tumor metastasis. **B,** Potentially therapeutic antimetastatic agents. Remodeling of the extracellular matrix is necessary for tumor growth and metastasis. The complex metastatic process involves several steps: vascular invasion (intravasation), circulation, extravasation, and proliferation at distant sites. Inhibition of any one of these steps could result in stabilization of the tumor. Matrix metalloproteinases are key for both intravasation and extravasation. Scientists have accelerated the discovery of a variety of agents with antimetastatic activity [68], specifically those opposing matrix metalloproteinase activity (*ie*, batimastat, marimistat, AG3340, CGS-27023A, and COL-3).

Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases

Matrix metalloproteinases
- Collagenases (MMP-1, -8, -13)
- Gelatinases (MMP-2, -9)
- Stromelysins (MMP-3, -7, -10, -11, -12)
- Membrane-type

Tissue inhibitors of metalloproteinases
- Soluble (TIMP-1, -2, -4)
- Associated with extracellular matrix (TIMP-4)

FIGURE 15-31. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Imbalances between MMPs and TIMPs promote tumor growth and metastasis. Destruction of the extracellular matrix is postulated to occur when local concentrations of MMP exceed those of TIMPs [69]. Numerous MMPs have been identified and can be divided into four subgroups: interstitial collagenases, gelatinases, stromelysins, and membrane-type MMPs [70]. The physiologic role for each of these enzymes is not completely understood, but MMP2 and MMP9 appear to be important in tumor growth; both of these enzymes are expressed in prostate cancer cells.

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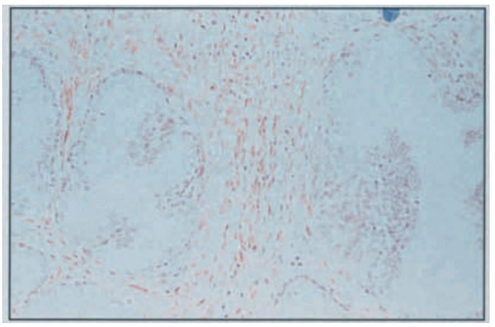

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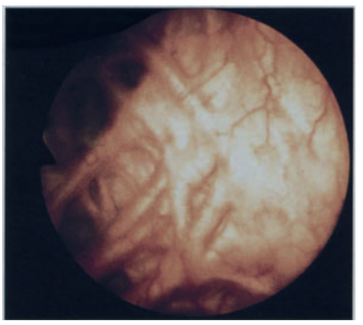

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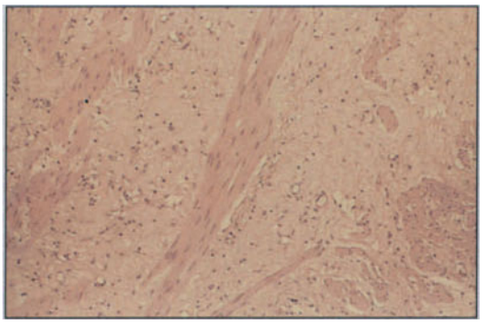

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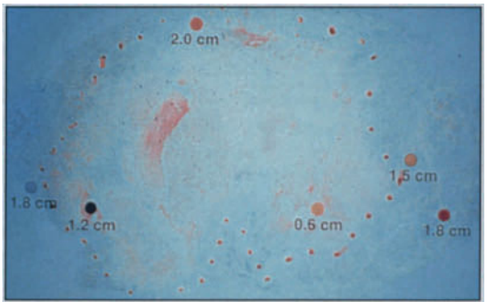

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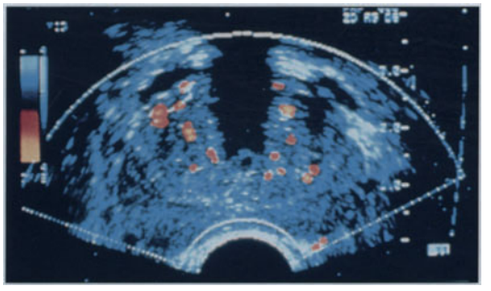

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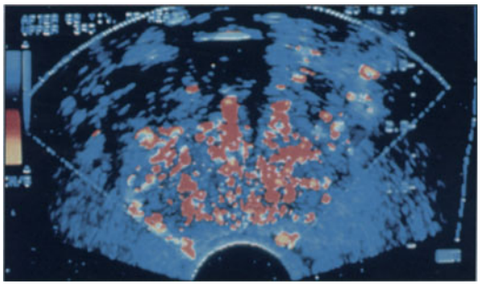

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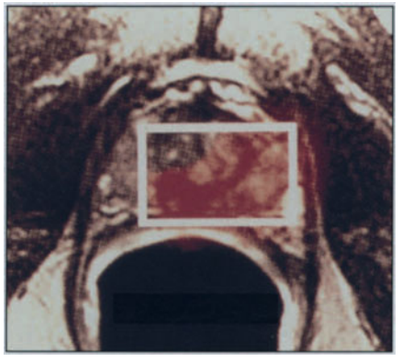

FIGURE 14-24A.